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(54) Urea derivatives and their use as acat inhibitors

Urea-Derivate und ihre Verwendung als ACAT-hemmenden Verbindungen
Dérivés d'urea et leur utilisation comme inhibiteurs d'ACAT

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(56) References cited: EP-A- 0 344 425, EP-A- 0 370 740, EP-A- 0 450 660, EP-A- 0 477 778, EP-A- 0 527 458

Remarks: The file contains technical information submitted after the application was filed and not included in this specification

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EP 0 625 507 B1

Description

FIELD OF THE INVENTION

5 This invention relates to new urea derivatives, processes for their preparation and their use in medicine. More particularly, the invention relates to compounds having an inhibitory activity against an acyl coenzyme A cholesterol acyl-transferase (called hereafter ACAT) and having a protective ability against an oxidative modification of low density lipoprotein (called hereafter LDL).

10 BACKGROUND OF THE INVENTION

In recent years, interest has been directed to the relationship between increase in the level of cholesterol in the serum and human health. It has been pointed out that the level of cholesterol in the serum is associated with the amount of cholesterol deposited in the blood vessel system and the deposition of cholesterol in the blood vessel system brings about e.g. coronary artery lesion, which is responsible for ischemic heart disease.

15 Drugs for reducing the level of cholesterol in the serum have been developed. These drugs, however, were effective in controlling blood cholesterol to an appropriate level, but ineffective in inhibiting absorption of cholesterol from the digestive tracts and deposition of cholesterol on the wall of blood vessels.

ACAT is an enzyme that catalyzes the synthesis of cholesteryl esters from acyl coenzyme A and cholesterol and plays an important role in cholesterol metabolism and its absorption from the digestive tracts. It is believed that ACAT occurs in the site of mucosa cells of intestinal tracts and is active in esterification and incorporation of cholesterol derived from the diet. On the other hand, the cholesterol deposited on the wall of blood vessels is the esterified cholesterol. The cholesterol accumulated in the foam cells which plays an important role in the formation of atherosclerosis lesion is also esterified cholesterol. The enzyme that catalyzes the esterification of cholesterol in these sites is also

25 ACAT. Accordingly, the inhibition of ACAT activity can result in inhibiting the incorporation in vivo of cholesterol derived from the diet and further the formation of cholesteryl ester in specified cell sites.

Compounds having an ACAT inhibitory activity are disclosed in EP 0450660 A1 and EP 0477778 A2. However, those known compounds have only an ACAT inhibitory activity and give no effect on the oxidative modification of LDL causing the foam cell transformation of macrophage which is an important phenomenon for the formation of atherosclerosis lesion.

The foam cells which play an important role in the formation of atherosclerosis lesion are products of uptake of oxidatively modified LDL into macrophage which results in the foam cell transformation of the macrophage. It is reported by Diane W. Morel et al. (Atheroma, Vol. 4, pages 357-364, 1984) that, the oxidatively modified LDL causes foam cell transformation of macrophage and plays an important role in the formation of atherosclerosis lesion. A report of TORU KITA et al. (Proc. Natl. Acad. Sci. USA, Vol. 84, pages 5928-5931, 1987) demonstrates that prevention of the oxidative modification of LDL induces regression of the atherosclerosis lesion. Therefore, inhibition of the oxidative modification of LDL, in addition to the above-mentioned ACAT inhibitory activity, is very important in preventing the formation and progression as well as inducing regression of atherosclerosis lesion.

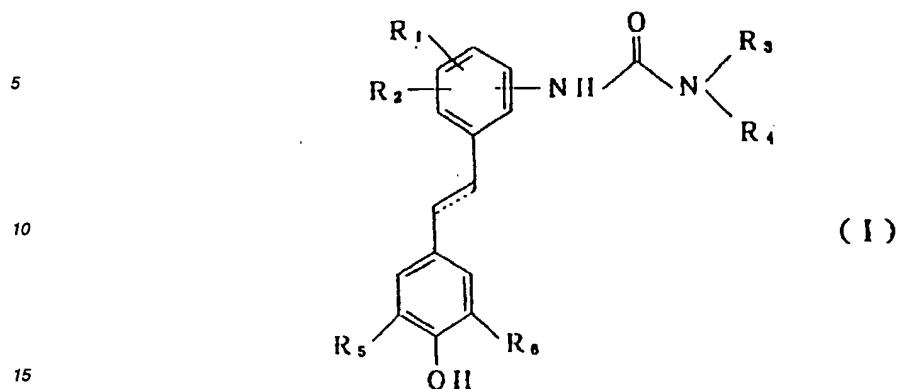
40 Under such circumstances, it has been desired to develop compounds having an ACAT inhibitory activity and capable of inhibiting an oxidative modification of LDL or the like, since such compounds may decrease the serum cholesterol level and inhibit the oxidative modification of LDL cholesterol deposited on the blood vessel or tissue, thus being effective for inhibiting the formation and progression of atherosclerosis lesions and inducing its regression.

EP-A-0 527 458 discloses certain new 3,5-di-tert-butyl-4-hydroxyphenyl derivatives which are described as having antioxidant activity and being capable of inhibiting ACAT-dependent esterification. The compounds disclosed are described as being useful as medicaments, especially as anti-atherosclerotics.

DETAILED DESCRIPTION OF THE INVENTION

50 We have now found new urea derivatives which exhibit both an ACAT inhibitory activity and an antioxidative activity. The urea derivatives of the present invention possess an ACAT inhibitory activity, thereby inhibiting absorption of cholesterol from the intestinal tracts, lowering blood cholesterol level and inhibiting accumulation of cholesteryl esters in the wall of blood vessels, atheroma and macrophage, and simultaneously an antioxidative activity i.e. a protective activity against the oxidative modification of LDL which participates in foam cell transformation of macrophage thereby effectively inhibiting the formation and progression of atherosclerosis lesion and inducing its regression.

55 According to one aspect of the present invention, there is provided a compound of formula (I) and pharmaceutically acceptable salts thereof, which exhibits both an ACAT inhibitory activity and an antioxidative activity.



in which:

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R_1 and R_2 , which may be the same or different, each represents

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- a hydrogen atom,
- a halogen atom,
- a straight or branched (C₁-C₆)alkyl group or
- a straight or branched (C₁-C₆)alkoxy group,

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R_3 and R_4 , which may be the same or different, each represents

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- a hydrogen atom,
- a straight or branched (C₁-C₁₂)alkyl group,
- a straight or branched (C₂-C₂₀)alkenyl group,
- a (C₁-C₆)alkoxy(C₁-C₆)alkyl group,
- a (C₁-C₆)alkoxycarbonyl(C₁-C₉)alkyl group,
- a benzyloxycarbonyl(C₁-C₆)alkyl group in which the alkyl moiety is optionally substituted by phenyl,
- a N,N-di(C₁-C₆)alkylamino(C₁-C₆)alkyl group,
- a N-(C₁-C₆)alkyl-N-benzylamino(C₁-C₆)alkyl group,
- a (C₁-C₆)alkylthio(C₁-C₆)alkyl group,
- an oxo(C₁-C₉)alkyl group,
- a hydroxy(C₁-C₆)alkyl group,
- a dihydroxy(C₁-C₆)alkyl group,
- a cyclo(C₃-C₁₅)alkyl group,
- a cyclo(C₃-C₈)alkyl(C₁-C₆)alkyl group,
- a dicyclo(C₃-C₉)alkyl(C₁-C₆)alkyl group,

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a bicyclo(C₆-C₉)alkyl group,

a tricyclo(C₉-C₁₂)alkyl group,

in which in all cases the cycloalkyl group or the cycloalkyl moiety is optionally substituted by one or two substituents selected from the group consisting of (C₁-C₆)alkyl, hydroxy, amino, acetoxy, acetamido, phenyl, benzyloxy, dimethylaminophenyl, and methylenedioxyphenyl, which may be further fused with a benzene ring,

an aryl group,

an aryl(C₁-C₆)alkyl group,

a diaryl(C₁-C₆)alkyl group,

in which in all cases the aryl group or the aryl moiety is optionally substituted by one, two or three substituents selected from the group consisting of (C₁-C₆)alkyl, (C₁-C₆)alkoxy, halogen, nitro, hydroxy, amino, dimethylamino, methylenedioxy, and pyrrolidinyl,

a heterocyclic group or

a heterocyclic group attached to a (C₁-C₆)alkylene chain,

in which in all cases the heterocyclic group represents a saturated or unsaturated, 5 to 8 membered ring monocyclic or bicyclic, heterocyclic group containing 1 to 3 heteroatoms selected from the group consisting of S, O and N, and the heterocyclic group is optionally substituted by one or two substituents selected from the group consisting of acetyl, hydroxy, (C₁-C₉)alkyl, (C₁-C₉)alkoxy, cyclo(C₃-C₈)alkyl, cyclo(C₃-C₈)alkyl(C₃-C₁₀)alkyl, pyridyl(C₁-C₆)alkyl, phenyl, phenyl(C₁-C₆)alkyl, diphenyl(C₁-C₆)alkyl, and phenylpiperazinyl, the phenyl group or the phenyl moiety being optionally substituted by one or two substituents selected from the group consisting of halogen, hydroxy, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, cyano, diethylamino and trifluoromethyl, which may be further fused with a benzene ring,

and further R₃ and R₄, together with the nitrogen atom to which they are attached, may form a saturated or unsaturated heterocyclic group,

in which the heterocyclic group represents a 5 to 8 membered ring monocyclic or bicyclic, heterocyclic group or a group derived from a heterocyclic spiro compound, which may contain one or two heteroatoms selected from the group consisting of S, O or N, the heterocyclic group being optionally substituted by one or two substituents selected from the group consisting of (C₁-C₆)alkyl, hydroxy, hydroxy(C₁-C₆)alkyl, (C₁-C₆)alkoxy(C₁-C₆)alkyl, acetoxy(C₁-C₆)alkyl, (C₁-C₉)alkylcarbonyl, (C₁-C₆)alkoxycarbonyl, amino, tosyl, phenyl, halogenophenyl, (C₁-C₆)alkoxyphenyl, phenyl(C₁-C₆)alkyl, benzyloxy, benzyloxy(C₁-C₆)alkyl, tolyl, xylyl, benzoyl, methylenedioxyphenyl(C₁-C₆)alkyl, pyridyl, pyridylcarbonyl, piperidyl, pyrrolidinyl(C₁-C₆)alkyl and pyrrolidinylcarbonyl(C₁-C₆)alkyl, which may be further fused with a benzene ring,

in which in all cases the alkyl and alkoxy moieties may be either straight or branched,

with the proviso that both R₃ and R₄ do not represent a hydrogen atom at the same time;

R₅ and R₆, which may be the same or different, each represents a straight or branched (C₁-C₆)alkyl group; and the line



represents -CH₂CH₂- or -CH=CH-.

Referring to R₁ and R₂ in formula (I), the halogen atom includes fluorine, chlorine, bromine and iodine, the (C₁-C₆)alkoxy group includes e.g. methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, pentyloxy and hexyloxy, and the (C₁-C₆)alkyl group includes e.g. methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl and hexyl.

Referring to R₃ and R₄ in formula (I), the (C₁-C₁₂)alkyl group includes e.g. methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, isoheptyl, heptyl, octyl, trimethylpentyl, 2,4,4-trimethyl-2-pentyl, nonyl, decyl and dodecyl. The (C₂-C₂₀)alkenyl group includes e.g. vinyl, allyl, isopropenyl, 2-butenyl, 2-pentenyl, 4-pentenyl, 3-hexenyl, 5-hexenyl, 4-octenyl, 7-octenyl, 7-decenyl, 3,7-dimethyl-2,6-octadienyl, 10-tetradecenyl, 8-heptadecenyl, 8-octadecenyl and 4,7,10,13,16-nonadecapentaenyl. The (C₁-C₆)alkoxy(C₁-C₆)alkyl group includes e.g.

2-methoxyethyl, 4-methoxybutyl, 2-methoxybutyl, 6-methoxyhexyl, ethoxymethyl, 3-ethoxypropyl, 2-propoxyethyl, 5-propoxypropyl, isopropoxymethyl, butoxymethyl, 2-isobutoxyethyl, sec-butoxymethyl, tert-butoxymethyl, pentyloxymethyl, 2-pentyloxyethyl and hexyloxymethyl.

The (C₁-C₆)alkoxycarbonyl(C₁-C₉)alkyl group includes e.g. 2-(methoxycarbonyl)ethyl, 7-(methoxycarbonyl)heptyl, 2-(ethoxycarbonyl)ethyl, 4-(ethoxycarbonyl)butyl, propoxycarbonylmethyl, 3-(propoxycarbonyl)butyl, isopropoxycarbonylmethyl, butoxycarbonylmethyl, 1-(butoxycarbonyl)ethyl, 2-(isobutoxycarbonyl)ethyl, sec-butoxycarbonylmethyl, 2-(tert-butoxycarbonyl)ethyl, pentyloxycarbonylmethyl and 2-(hexyloxycarbonyl)ethyl, α -(methoxycarbonyl)benzyl, α -(ethoxycarbonyl)benzyl.

The benzyloxycarbonyl(C₁-C₆)alkyl group includes benzyloxycarbonylmethyl, 2-(benzyloxycarbonyl)ethyl, 6-(benzyloxycarbonyl)hexyl, 4-(benzyloxycarbonyl)butyl and α -(benzyloxycarbonyl)benzyl.

The N,N-di(C₁-C₆)alkylamino(C₁-C₆)alkyl group includes e.g. 2-(N,N-dimethylamino)ethyl, 4-(N,N-dimethylamino)butyl, 2-(N,N-diethylamino)ethyl, 3-(N,N-diethylamino)propyl, N,N-diisopropylaminomethyl, N,N-dibutylaminomethyl, 2-(N,N-dibutylamino)ethyl, 2-(N,N-diisobutylamino)ethyl, N,N-dipentylaminomethyl, 2-(N,N-diisohexylaminomethyl)ethyl and N,N-diisohexylaminomethyl.

The N-(C₁-C₆)alkyl-N-benzylamino(C₁-C₆)alkyl includes e.g. 2-(N-benzyl-N-methylamino)ethyl, 2-(N-benzyl-N-ethylamino)ethyl, 4-(N-benzyl-N-methylamino)butyl, 2-(N-benzyl-N-ethylamino)ethyl and 3-(N-benzyl-N-ethylamino)propyl.

The (C₁-C₆)alkylthio(C₁-C₆)alkyl group includes e.g. 2-(methylthio)ethyl, 2-(ethylthio)ethyl, propylthiomethyl, 2-(isopropylthio)ethyl, 1-(butylthio)ethyl, isobutylthiomethyl, tert-butylthiomethyl, pentylthiomethyl and hexylthiomethyl.

The oxo(C₁-C₆)alkyl group includes e.g. 2-oxopropyl, 2-oxobutyl, 4-oxopentyl, 6-oxoheptyl and 2-oxooctyl.

The hydroxy(C₁-C₆)alkyl group includes e.g. 2-hydroxyethyl, 2-hydroxypropyl, 3-hydroxypropyl, 3-hydroxybutyl and 6-hydroxyhexyl.

The dihydroxy(C₁-C₆)alkyl group includes e.g. 2,3-dihydroxypropyl, 4,5-dihydroxypentyl, 1,5-dihydroxy-3-pentyl, 2-ethyl-1,3-dihydroxy-2-propyl, and 2,4-dihydroxy-3-methylpentyl.

The cyclo(C₃-C₁₅)alkyl group includes e.g. cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclodecyl, cyclododecyl, 1-phenylcyclopentyl, 4-(benzyloxy)cyclohexyl, 4-aminocyclohexyl, 4-acetamidocyclohexyl, 4-hydroxycyclohexyl, 4-acetoxycyclohexyl, 4-tert-butylcyclohexyl, 2,3-dimethylcyclohexyl, 1,2,3,4-tetrahydronaphthyl, cyclododecyl and benzyloxycyclohexyl.

The cyclo(C₃-C₈)alkyl(C₁-C₈)alkyl group includes e.g. cyclopropylmethyl, 2-cyclobutylethyl, 2-cycloheptylethyl, cyclohexylmethyl, 3-cyclohexylpropyl, 4-cyclohexylbutyl, cyclooctylmethyl, 5-cyclooctylpentyl, 1-(4-dimethylaminophenyl)cyclopentylmethyl and 1-(3,4-methylenedioxyphenyl)cyclopentylmethyl.

The dicyclo(C₃-C₉)alkyl(C₁-C₆)alkyl group includes e.g. dicyclohexylmethyl, 2,2-dicyclohexylethyl and 3,3-dicyclohexylpropyl.

The bicyclo(C₆-C₉)alkyl group includes e.g. bicyclo[3.3.0]-2-octyl, bicyclo[3.3.1]-2-nonyl and bicyclo[3.2.1]-2-octyl.

The tricyclo(C₉-C₁₂)alkyl group includes e.g. tricyclo[5.2.1.0^{2,6}]decyl and tricyclo[3.3.1.1^{3,7}]decyl.

The aryl group includes e.g. phenyl, 1-naphthyl, 2-naphthyl, 3-naphthyl, 4-methylphenyl, 2,6-diisopropylphenyl, 3,5-di-tert-butyl-4-hydroxyphenyl, 2-methoxyphenyl, 4-hexyloxyphenyl, 4-fluorophenyl, 2-nitrophenyl, 4-chloronaphthyl, 3-amino-2-naphthyl, 5-hydroxynaphthyl, 5-methoxynaphthyl and anthryl.

The aryl(C₁-C₆)alkyl group includes e.g. benzyl, phenethyl, α -methylbenzyl, 3-phenylpropyl, 4-phenylbutyl, 9-anthrylmethyl, 4-ethylbenzyl, 4-ethoxybenzyl, 4-fluorobenzyl, 3,4-methylenedioxybenzyl, 3,4,5-trimethoxybenzyl, 4-methylphenethyl, 2-methoxyphenethyl, 4-methoxyphenethyl, 3,4-dimethoxyphenethyl, 3-chlorophenethyl, 4-chlorophenethyl, 4-fluorophenethyl, 4-nitrophenethyl, 3,4,5-trimethoxyphenethyl, 4-nitrophenylbutyl, 1-(4-fluorophenyl)-2-methylpropyl, 3-(3,4-dichlorophenyl)propyl, 4-dimethylaminophenethyl, 2-(3,4-dichlorophenyl)-2-propyl, 2-(3,4-dichlorophenyl)-2-methylpropyl, 2-(2-fluorophenyl)-2-methylpropyl, 2-(3-fluorophenyl)-2-methylpropyl, 2-(4-fluorophenyl)-2-methylpropyl and 2-[4-(1-pyrrolidinyl)phenyl]-2-methylpropyl.

The diaryl(C₁-C₆)alkyl group includes e.g. diphenylmethyl, 1,2-diphenylethyl, 2,2-diphenylethyl, 4,4-diphenylbutyl and 6,6-diphenylhexyl.

The monocyclic, heterocyclic group includes e.g. 3-furyl, 2-thienyl, 3-pyrrolyl, 2-pyrrolidinyl, 2H-pyran-3-yl, 2-pyridyl, 4-piperidyl, 3-morpholinyl, 2-piperazinyl, 1-methyl-4-piperidyl, 1-benzyl-4-piperidyl, 1-methyl-3-piperidyl, 1-(2,4-difluorobenzyl)-4-piperidyl, 1-(3,4-difluorobenzyl)-4-piperidyl, 1-(3,5-difluorobenzyl)-4-piperidyl, 1-[2,4-bis(trifluoromethyl)benzyl]-4-piperidyl, 1-(4-methoxybenzyl)-4-piperidyl, 1-phenethyl-4-piperidyl, 1-(2-fluorobenzyl)-4-piperidyl, 1-(3-fluorobenzyl)-4-piperidyl, 1-(4-fluorobenzyl)-4-piperidyl, 1-(4-chlorobenzyl)-4-piperidyl, 1-(4-cyanobenzyl)-4-piperidyl, 1-(2-pyridylmethyl)-4-piperidyl, 1-(3-pyridylmethyl)-4-piperidyl, 1-(4-pyridylmethyl)-4-piperidyl, 1-[4-(N,N-diethylamino)benzyl]-4-piperidyl, 1-[bis(4-fluorophenyl)methyl]-4-piperidyl, 1-(4-fluorophenethyl)-4-piperidyl, 1-(2,4-dimethylbenzyl)-4-piperidyl, 1-acetyl-4-piperidyl, 1-(4-hydroxybenzyl)-4-piperidyl, 1-(3,4-dihydroxybenzyl)-4-piperidyl, 1-ethyl-4-piperidyl, 1-neopentyl-4-piperidyl, 1-cyclohexyl-4-piperidyl, 1-heptyl-4-piperidyl, 1-(2-propyl)-4-piperidyl, 1-benzyl-3-piperidyl, 2-phenyl-3-piperidyl, 1-cyclohexylmethyl-3-piperidyl, 1-benzyl-3-pyrrolidinyl, 2-methoxy-5-pyridyl, 2-(4-phenyl-1-piperazinyl)-5-pyridyl and 5,6-dimethyl-1,2,4-triazin-3-yl.

The bicyclic, heterocyclic group includes e.g. 3-indolyl, 5-indazolyl, 2-quinolyl, 5-isoquinolyl, 2,4-dimethyl-1,8-naph-

thyridin-7-yl, 3,9-dimethyl-3,9-diazabicyclo[3.3.1]-7-nonyl, 9-methyl-3-oxa-9-azabicyclo[3.3.1]-7-nonyl, 9-(4-fluorobenzyl)-3-oxa-9-azabicyclo[3.3.1]-7-nonyl, 9-methyl-3-thia-9-azabicyclo[3.3.1]-7-nonyl, 8-methyl-8-azabicyclo[3.2.1]-3-octyl and 1-azabicyclo[2.2.2]-3-octyl.

The heterocyclic group attached to an alkylene chain may be the above-mentioned monocyclic or bicyclic heterocyclic group attached to an alkylene chain, which includes e.g. 3-furylmethyl, 3-(2-thienyl)propyl, 2-(3-indolyl)ethyl, 2-(3-pyrrolyl)ethyl, 2-pyrrolidinylmethyl, 2-pyridylmethyl, 3-pyridylmethyl, 4-pyridylmethyl, 2-(2-pyridyl)ethyl, 2-(4-piperidyl)ethyl, 3-(3-morpholinyl)propyl, 3-indolylmethyl, 2-(5-indazolyl)ethyl, 2-quinolylmethyl, 3-(1-imidazolyl)propyl, 2-morpholinoethyl, 3-morpholinopropyl, 3-(2-methylpiperidyl)propyl, 2-(1-pyrrolidinyl)ethyl, [4-(4-fluorobenzyl)-3-morpholinyl]methyl and (1-benzyl-4-hydroxy-4-piperidyl)methyl.

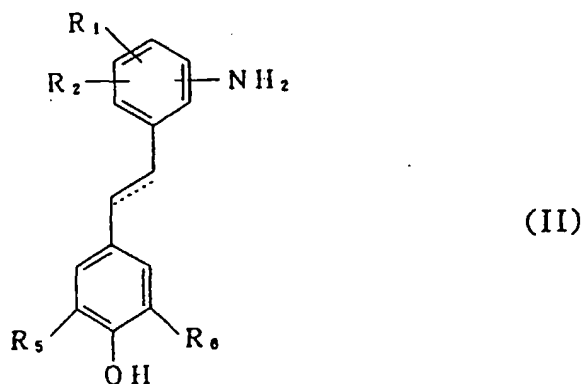
When R_3 and R_4 in formula (I), together with the nitrogen atom to which they are attached form the heterocyclic ring, the monocyclic, heterocyclic group includes e.g. pyrrolidinyl, 2,5-dimethyl-1-pyrrolidinyl, 3-hydroxy-1-pyrrolidinyl, 2-hydroxymethyl-1-pyrrolidinyl, 2-hydroxyethyl-1-pyrrolidinyl, 2-methoxymethyl-1-pyrrolidinyl, 2-(1-pyrrolidinylmethyl)pyrrolidinyl, 3-pyrrolin-1-yl, 2,5-dimethyl-3-pyrrolin-1-yl, piperidino, 2-methylpiperidino, 2-ethylpiperidino, 3-methylpiperidino, 4-methylpiperidino, 4-piperidinopiperidino, 3,3-dimethylpiperidino, 2,6-dimethylpiperidino, 3,5-dimethylpiperidino, 2,4-dimethylpiperidino, 2-(hydroxymethyl)piperidino, 2-(2-hydroxyethyl)piperidino, 2-(2-acetoxyethyl)piperidino, 3-hydroxypiperidino, 4-hydroxypiperidino, 4-oxopiperidino, 4-aminopiperidino, 4-benzylpiperidino, 2-[2-(benzyloxy)ethyl]piperidino, 3-(benzyloxy)piperidino, 1,2,3,6-tetrahydropyridyl, perhydroazepinyl, perhydroazocinyl, piperazinyl, 4-methyl-1-piperazinyl, 3-methyl-1-piperazinyl, 3,5-dimethyl-1-piperazinyl, 2,5-dimethyl-1-piperazinyl, 4-(2-hydroxyethyl)-1-piperazinyl, 4-pentanoyl-1-piperazinyl, 4-acetyl-1-piperazinyl, 4-p-toluenesulfonyl-1-piperazinyl, 4-benzyl-1-piperazinyl, 4-(3,4-methylenedioxybenzyl)-1-piperazinyl, 4-(2-pyridyl)-1-piperazinyl, 4-nicotinoyl-1-piperazinyl, 4-(1-pyrrolidinylcarbonylmethyl)-1-piperazinyl, 4-benzyl-1-piperidyl, 4-phenyl-1-piperidyl, 4-phenyl-1,2,3,6-tetrahydropyridyl, 4-phenyl-1-piperazinyl, 4-benzyl-1-piperazinyl, 4-(o-tolyl)-1-piperazinyl, 4-(2-fluorophenyl)-1-piperazinyl, 4-(2,3-xylyl)-1-piperazinyl, 4-(2-chlorophenyl)-1-piperazinyl, 4-(2-methoxyphenyl)-1-piperazinyl, 4-(2-ethoxyphenyl)-1-piperazinyl, 4-(m-tolyl)-1-piperazinyl, 4-(3,4-difluorophenyl)-1-piperazinyl, 4-(4-chlorophenyl)-1-piperazinyl, 4-(3,4-dimethoxyphenyl)-1-piperazinyl, homopiperazinyl, morpholino, 2,6-dimethylmorpholino, thiazolidinyl, thiomorpholino, pyrrolyl, 2-ethyl-1-pyrrolyl, 2,5-dimethyl-1-pyrrolyl, pyrazolyl, 3-methyl-1-pyrazolyl, 4-methyl-1-pyrazolyl, imidazolyl, 4-methyl-1-imidazolyl, 4-phenyl-1-imidazolyl, 1H-1,2,3-triazol-1-yl, 1,2,4-triazol-1-yl, imidazolidinyl, 2-imidazolin-1-yl, pyrazolidinyl and 2-pyrazolin-1-yl.

The bicyclic, heterocyclic group includes e.g. 4,5,6,7-tetrahydroindol-1-yl, 1,5,6,7-tetrahydro-4-oxoindol-1-yl, indolinyl, isoindolinyl, perhydroindol-1-yl, decahydroquinolinyl, perhydroisoquinolin-2-yl, 1,2,3,4-tetrahydrocarbazol-1-yl, 1,2,3,4-tetrahydroquinolin-1-yl, 1,2,3,4-tetrahydroisoquinolin-1-yl, 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl, 5H-dibenz[b,f]azepin-5-yl, 10,11-dihydro-5H-dibenz[b,f]azepin-5-yl, 3-azabicyclo[3.2.2]nonan-3-yl, 3-methyl-3,9-diazabicyclo[3.3.1]nonan-9-yl, 3-oxa-9-azabicyclo[3.3.1]nonan-9-yl and 3-thia-9-azabicyclo[3.3.1]nonan-9-yl.

The group derived from the heterocyclic spiro compound includes e.g. 1,4-dioxa-8-azaspiro[4.5]decan-8-yl, 1,4-dioxa-7-azaspiro[4.4]decan-7-yl, 1,5-dithia-9-azaspiro[5.5]undecan-9-yl and 1-phenyl-4-oxo-1,3,8-triazaspiro[4.5]decan-8-yl.

It should be understood that the compounds of formula (I) include all of their possible isomers including stereoisomer, metabolite, metabolic precursor and metabolic intermediate.

The compounds of formula (I) can be prepared by various conventional procedures as described below. The compounds of formula (I) are prepared by reacting a compound of formula (II)



wherein R_1 and R_2 as well as R_5 and R_6 are as defined above, and

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denotes -CH₂-CH₂- or -CH=CH- with an isocyanate of formula (III)

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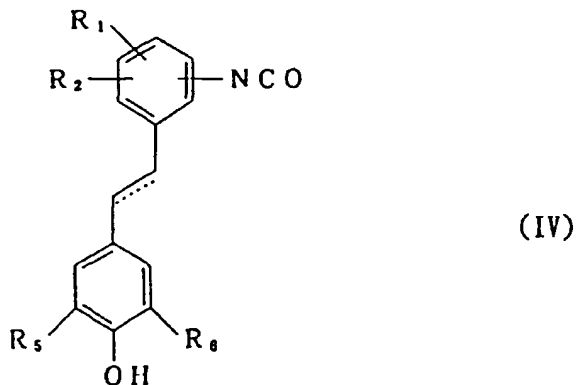


wherein R denotes R₃ or R₄, and R₃ and R₄ are as defined above in an organic solvent under ice-cooling or at a temperature up to room temperature. This reaction is performed using the compound of formula (III) in an amount of 0.1 to 10 moles, preferably 0.5 to 2 moles per mole of the compound of formula (II).

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Alternatively, the compounds of formula (I) are prepared by reacting an isocyanate of formula (IV)

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wherein R₁ and R₂ as well as R₅ and R₆ are as defined above, and

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denotes -CH₂-CH₂- or -CH=CH- with an amine of formula (V)

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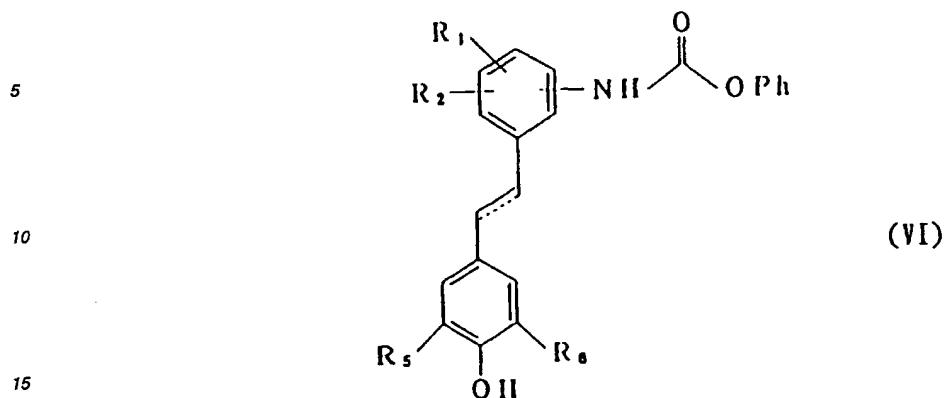


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wherein R denotes R₃ or R₄, and R₃ and R₄ are as defined above in an organic solvent under ice-cooling or at a temperature up to room temperature. This reaction is performed using the compound of formula (V) in an amount of 0.1 to 10 moles, preferably 0.5 to 2 moles per mole of the compound of formula (IV).

Alternatively, the compounds of formula (I) are prepared by reacting a carbamate of formula (VI)

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wherein R_1 and R_2 as well as R_5 and R_6 are as defined above, and

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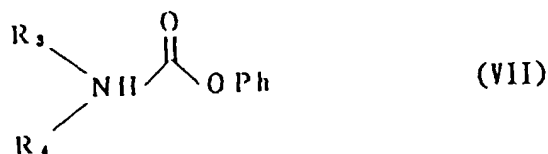
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denotes $-CH_2-CH_2-$ or $-CH=CH-$ with an amine of formula (V) wherein R denotes R_3 or R_4 , and R_3 and R_4 are as defined above in an organic solvent while heating at $50-150^\circ C$. This reaction is performed using the compound of formula (V) in an amount of 0.1 to 10 moles, preferably 0.5 to 2 moles per mole of the compound of formula (VI).

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Alternatively, the compounds of formula (I) are prepared by reacting a compound of formula (II) with a carbamate of formula (VII)

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wherein R denotes R_3 or R_4 , and R_3 and R_4 are as defined above in an organic solvent while heating to $50-150^\circ C$. This reaction is performed using the compound of formula (VII) in an amount of 0.1 to 10 moles, preferably 0.5 to 2 moles per mole of the compound of formula (II).

45

The isocyanates of formula (III) or (IV) are prepared, for example, by treating a carboxylic acid of formula $RCOOH$ wherein R denotes R_3 or R_4 , and R_3 and R_4 are as defined above or a derivative thereof with 1 to 10 moles, preferably 1 to 3 moles of diphenylphosphoryl azide, trimethylsilylazide or the like, per mole of the carboxylic acid, in an organic solvent to give an acyl azide, which is in turn subjected to a rearrangement reaction under heating at $50-150^\circ C$, or alternatively by reacting a compound of formula (V) or (II) with phosgen.

50

The carbamate of formula (VI) or (VII) are prepared by reacting a compound of formula (II) or (V) with 0.1 to 10 moles, preferably 0.5 to 2 moles of phenyl chloroformate per mole of the compound in an organic solvent under ice-cooling or at a temperature up to room temperature. This reaction may be conducted in the presence of an acid binder. The acid binders include e.g. inorganic basic substances such as sodium hydride, potassium hydroxide, sodium carbonate, potassium carbonate and organic basic substances including secondary amines such as diisopropylamine and tertiary amines such as triethylamine, methylmorpholine, pyridine.

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The organic solvents used in each of the above-described reactions include aliphatic hydrocarbon solvents such as hexane, petroleum ether and cyclohexane, aromatic hydrocarbon solvents such as benzene, toluene and xylenes, halogenated hydrocarbon solvents such as methylene chloride, chloroform, carbon tetrachloride and dichloroethane, ether solvents such as ethyl ether, isopropyl ether, tetrahydrofuran and dioxane, ketone solvents such as acetone and

methyl ethyl ketone, ethyl acetate, acetonitrile and N,N-dimethylformamide.

The process steps for the compounds of the invention according to the reactions as described above are shown in the following scheme 1:

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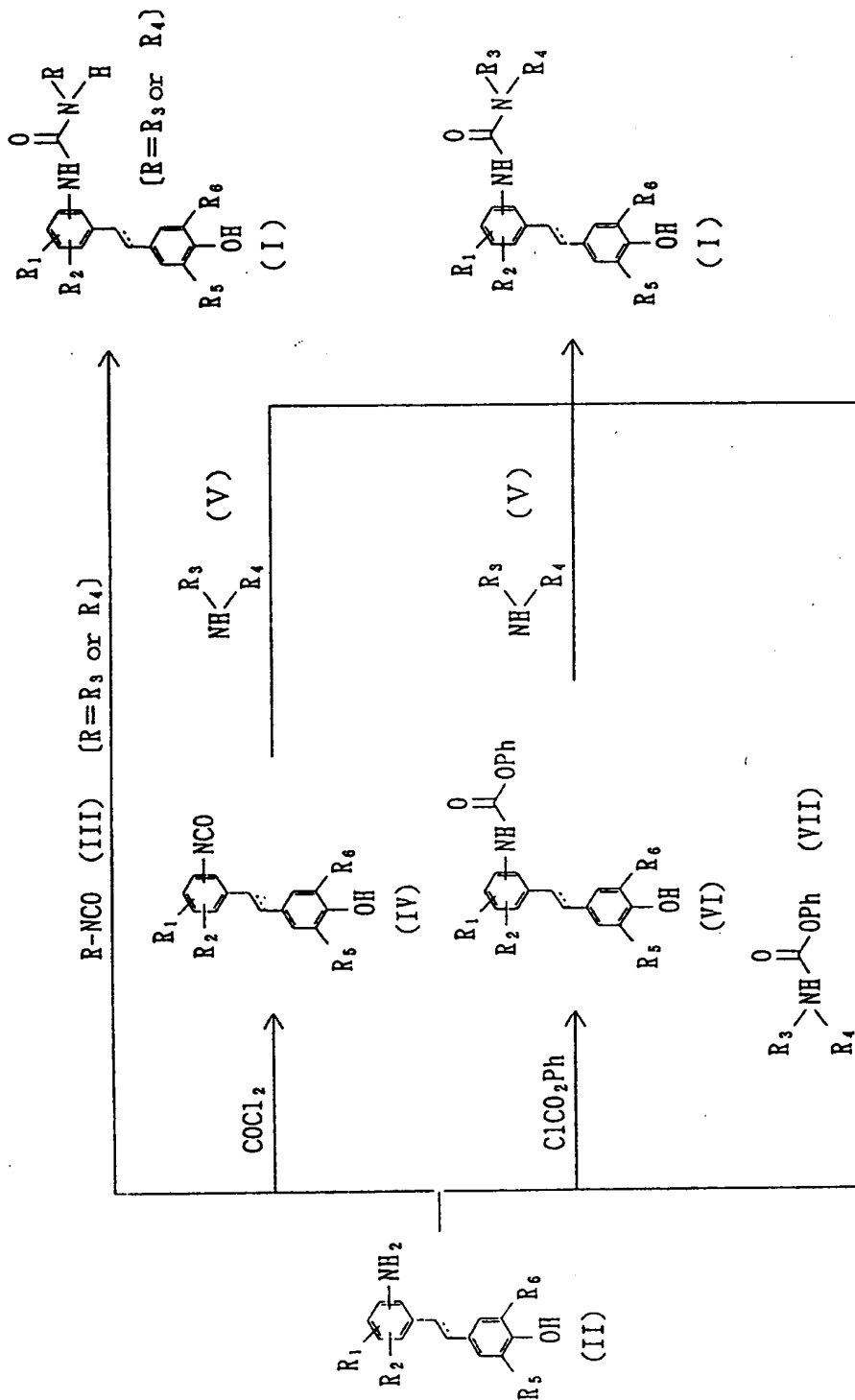
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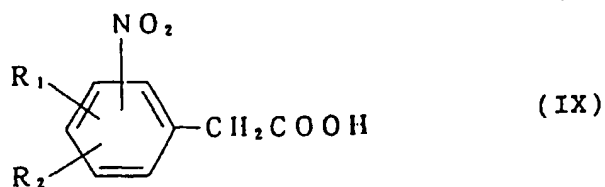
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Scheme 1



The compounds of formula (II) are prepared by reacting a nitrophenylacetic acid derivative of formula (IX)

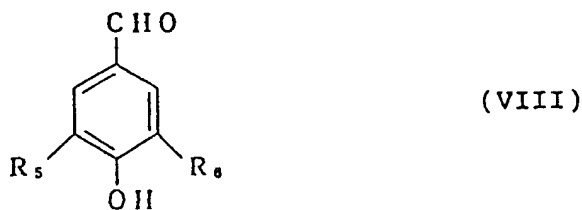
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wherein R₁ and R₂ are as defined above with a benzaldehyde derivative of formula (VIII)

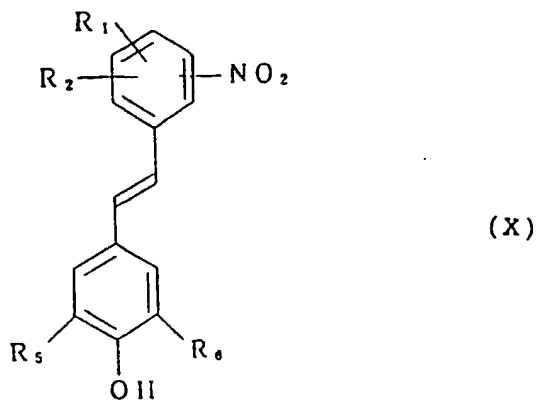
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25 wherein R₅ and R₆ are as defined above while heating at 100 to 200°C in the presence of a catalytic amount of a basic material such as piperidine, to form a compound of formula (X)

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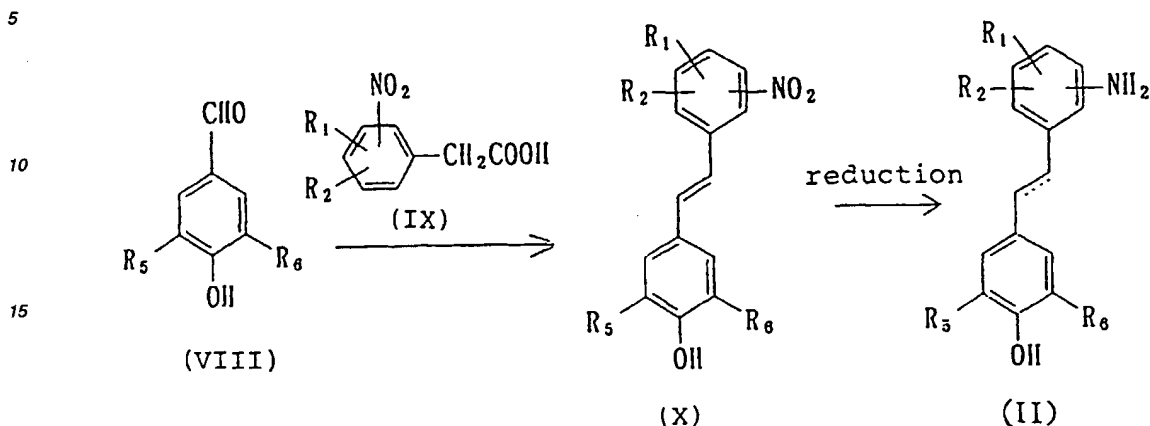
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45 wherein R₅ and R₆ are as defined above, followed by reduction. The reaction is performed using the compound of formula (VIII) in an amount of 0.1 to 10 moles, preferably 0.5 to 2 moles per mole of the compound of formula (IX). The reduction process includes e.g. that using zinc, iron, tin, stannous chloride or the like in an acidic solution such as hydrochloric acid, acetic acid or a catalytic hydrogenation using a catalyst such as palladium carbon, platinum oxide or the like. The process steps by the reactions as described above are shown in the following scheme 2:

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Scheme 2



25 Pharmaceutically acceptable salts of the compounds of formula (I) may be formed in conventional way. The acid addition salts may be formed for example by reaction of the base compound of formula (I) with a pharmaceutically acceptable inorganic acid such as hydrochloric, hydrobromic, hydroiodic, sulfuric and phosphoric acids or a pharmaceutically acceptable organic acid such as oxalic, maleic, fumaric, lactic, malic, citric, tartaric, benzoic and methanesulphonic acids.

30 The compounds of formula (I) according to the present invention possess both an ACAT inhibitor activity and an antioxidative activity, especially a protective ability against an oxidative modification of LDL. By the ACAT inhibitory activity, the present compounds can inhibit an absorption of cholesterol from the intestinal tracts, reduce a plasma cholesterol level and inhibit an accumulation of cholesteryl esters in the wall of blood vessels, atheroma lesion and macrophage. By the antioxidative activity, especially a protective activity against the oxidative modification of LDL, the present compounds can inhibit the formation and progression of atherosclerosis lesion and inducing its regression.

35 Thus, the compounds of the present invention are useful in the prophylaxis or treatment of hypercholesterolemia and atherosclerosis.

According to another aspect of the present invention, there is provided an ACAT inhibitor comprising the compound of formula (I) or a pharmaceutically acceptable salt thereof.

40 In further aspects, the present invention provides a pharmaceutical composition for the prophylaxis or treatment of hypercholesterolemia or atherosclerosis, which comprises as an active ingredient the compound of formula (I) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier and/or excipient.

45 The compounds of the invention can usually be administered orally or parenterally in the form of a pharmaceutical preparation. The pharmaceutical preparations include tablets, capsules, troches, syrups, granules, powders, injections, suspensions and the like. It may be in bilayered or multilayered tablet with other drugs. The tablets may also be coated with a conventional coating to form, e.g., sugar-coated, enteric-coated or film-coated tablets.

In preparing solid preparations, additives such as lactose, refined sugar, crystalline cellulose, corn starch, calcium phosphate, sorbitol, glycin, carboxymethylcellulose, gum arabic, polyvinylpyrrolidone, hydroxypropylcellulose, polyethylene glycol, stearic acid, magnesium stearate and talc are employed.

A vegetable or synthetic wax or fat or a similar base is used in preparing the semi-solid preparations.

50 As additives in preparing the liquid preparations are used, for example, sodium chloride, sorbitol, glycerin, olive oil, almond oil, propylene glycol and ethyl alcohol.

The active ingredient is contained in the formulation in an amount of 0.0001-100% by weight, suitably 0.001-50% by weight in the case of formulations for oral administration and 0.0001-10% by weight in the case of formulations for injection based on the weight of the preparations.

55 Route and dosage of administration for the compounds of the invention are not specifically limited and are appropriately chosen depending upon form of the formulation, age and sex of the patient, severity of the disease and other factors. Daily dosage of the active ingredient is 0.01-1000 mg. No adverse toxicological effects are indicated at any of the above dosage ranges.

The invention is further illustrated by the following examples.

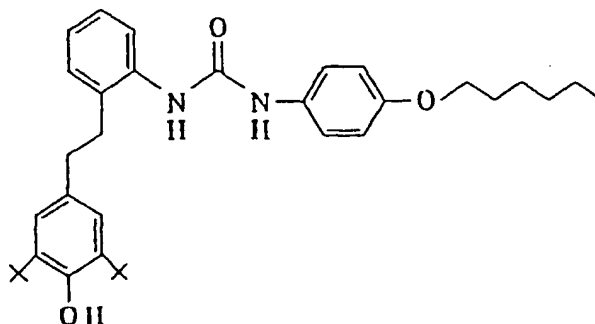
Example 1

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(4-hexyloxyphenyl)urea

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A solution of diphenylphosphorylazide (0.93 g, 3.4 mmol), 4-hexyloxybenzoic acid (0.68 g, 3.1 mmol) and triethylamine (0.34 g, 3.4 mmol) in toluene (10 ml) was stirred at room temperature for 3.5 hrs and heated at about 90°C for 2 hrs with stirring. After allowing the mixture to cool (under 0°C), a solution of 4-(2-aminophenethyl)-2,6-di-tert-butylphenol (1.0 g, 3.1 mmol) in toluene (4 ml) was added dropwise. The solution was warmed up to room temperature and stirred overnight. After distilling off the solvent and purification of the residue by a silica gel column chromatography, recrystallization from ethyl acetate/hexane afforded N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(4-hexyloxyphenyl)urea (1.2 g, 71% yield). m.p. 174-176°C

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¹H-NMR(δ ppm, CDCl₃) 7.40-7.42(m, 1H), 7.14-7.26(m, 5H), 6.81(s, 2H), 6.76-6.79(m, 2H), 5.98(s, 1H), 5.39(s, 1H), 5.13(s, 1H), 3.88(t, J=7Hz, 2H), 2.83-2.87(m, 2H), 2.76-2.80(m, 2H), 1.70-1.77(m, 2H), 1.38(s, 18H), 1.30-1.45(m, 6H), 0.87-0.93(m, 3H)
IR (cm⁻¹) 3640, 3310, 2950, 1630, 1560, 1490, 1440, 1230

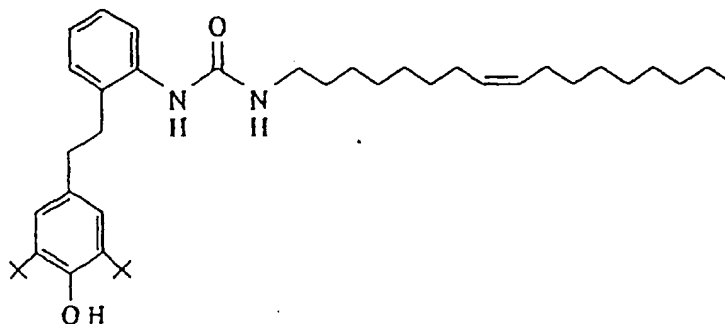
35 Example 2

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(8-heptadecenyl)urea

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The title compound was prepared in a similar manner to that mentioned in Example 1, using 9-octadecenoic acid instead of 4-hexyloxybenzoic acid.

¹H-NMR (δ ppm, CDCl₃) 7.16-7.26(m, 4H), 6.78(s, 2H), 5.29-5.34(m, 2H), 5.12(s, 1H), 5.00(s, 1H), 4.19(t, J=6Hz,

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1H), 3.11(dd, J=14, 6Hz, 2H), 2.77-2.87(m, 4H), 1.93-2.02(m, 4H), 1.38(s, 18H), 1.18-1.38(m, 25H)
IR (cm⁻¹) 3642, 3288, 2926, 1639, 1558, 1435, 1233, 750

Example 3

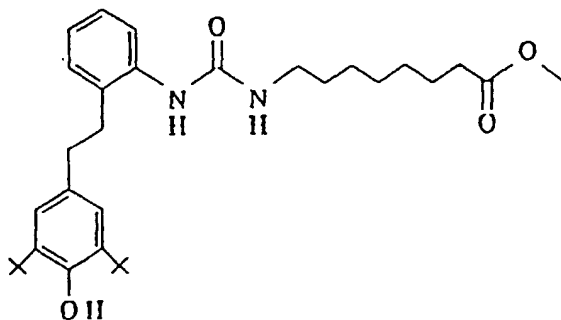
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N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(7-methoxycarbonylheptyl)urea

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The title compound was prepared in a similar manner to that mentioned in Example 1, using 8-methoxycarbonyl-
octanoic acid instead of 4-hexyloxybenzoic acid

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¹H-NMR (δ ppm, CDCl₃) 7.16-7.26(m, 4H), 6.78(s, 2H), 5.12(s, 1H), 4.98(s, 1H), 4.17(t, J=6Hz, 1H), 3.66(s, 3H),
3.09-3.14(m, 2H), 2.77-2.87(m, 4H), 2.28(t, J=8Hz, 2H), 1.53-1.61(m, 2H), 1.38(s, 18H), 1.18-1.30(m, 6H), 0.88(t,
J=7Hz, 2H)

IR (cm⁻¹) 3640, 2928, 1737, 1639, 1547, 1436, 1234

Example 4

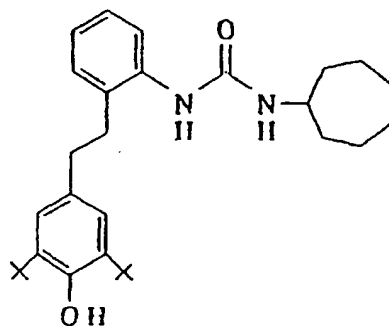
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N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-cycloheptylurea

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The title compound was prepared in a similar manner to that mentioned in Example 1, using cycloheptanecarboxylic
acid instead of 4-hexyloxybenzoic acid. m.p. 177-178°C

¹H-NMR (δ ppm, CDCl₃) 7.17-7.26(m, 4H), 6.79(s, 2H), 5.10(s, 1H), 5.05(bs, 1H), 4.19(d, J=8Hz, 1H), 3.75-3.85(m,
1H), 2.80-2.88(m, 2H), 2.75-2.80(m, 2H), 1.83-1.90(m, 2H), 1.38(s, 18H), 1.21-1.58(m, 10H)

IR (cm⁻¹) 3650, 3300, 2930, 2860, 1630, 1570, 1440, 1240

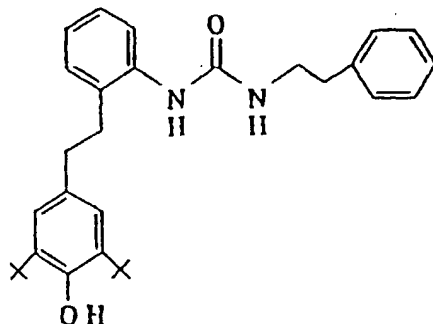
Example 5

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-phenethylurea

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The title compound was prepared in a similar manner to that mentioned in Example 1, using 3-phenylpropionic acid instead of 4-hydroxybenzoic acid.

m.p. 197-198°C

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$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.08-7.25(m, 9H), 6.76(s, 2H), 5.10(s, 1H), 5.00(s, 1H), 4.24(t, $J=6\text{Hz}$, 1H), 3.36-3.41(m, 2H), 2.72-2.80(m, 6H), 1.36(s, 18H)

IR (cm^{-1}) 3632, 3284, 2954, 1640, 1559, 1436, 1235, 748

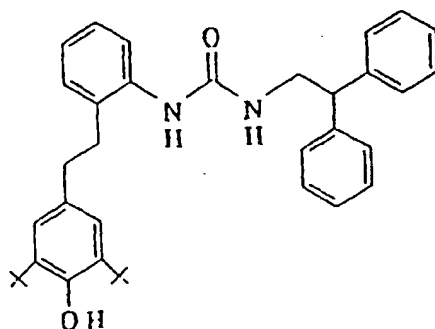
30 Example 6

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(2,2-diphenylethyl)urea

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The title compound was prepared in a similar manner to that mentioned in Example 1, using 3,3-diphenylpropionic acid instead of 4-hydroxybenzoic acid.

m.p. 179°C

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$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.09-7.44(m, 12H), 6.97-7.01(m, 1H), 6.78(d, $J=8\text{Hz}$, 1H), 6.72(s, 2H), 5.07(s, 1H), 4.93(s, 1H), 4.23(t, $J=6\text{Hz}$, 1H), 4.15(t, $J=8\text{Hz}$, 1H), 3.77(dd, $J=8, 6\text{Hz}$, 2H), 2.70(s, 4H), 1.35(s, 18H)

IR (cm^{-1}) 3644, 2930, 1650, 1553, 1510, 1234

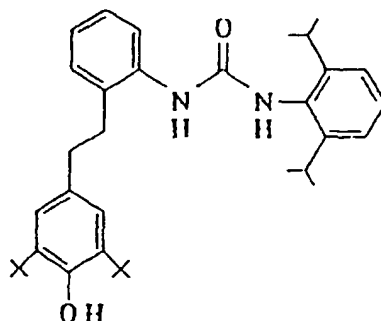
Example 7

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(2,6-diisopropylphenyl)urea

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The title compound was prepared in a similar manner to that mentioned in Example 1, using 2,6-diisopropylbenzoic acid instead of 4-hydroxybenzoic acid.

m.p. 209-210°C

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¹H-NMR (δ ppm, DMSO) 8.01(bs, 1H), 7.85(bs, 1H), 7.65(d, J=8Hz, 1H), 7.20-7.24(m, 1H), 7.10-7.14(m, 4H), 6.93-6.97(m, 3H), 6.62(s, 1H), 3.32-3.53(m, 1H), 3.18-3.25(m, 1H), 2.75-2.85(m, 4H), 1.37(s, 18H), 1.13(d, J=7Hz, 12H)
IR (cm⁻¹) 3612, 3320, 2958, 1646, 1586, 1534, 1435, 1231, 745

Example 8

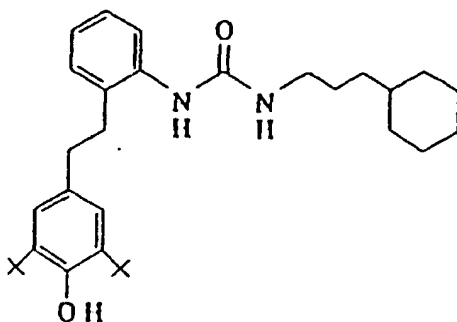
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N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(3-cyclohexylpropyl)urea

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The title compound was prepared in a similar manner to that mentioned in Example 1, using 4-cyclohexylbutanoic acid instead of 4-hydroxybenzoic acid.

m.p. 166°C

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¹H-NMR (δ ppm, CDCl₃) 7.18-7.26(m, 4H), 6.78(s, 2H), 5.11(s, 1H), 5.02(s, 1H), 4.20(t, 1H), 3.10 (dt, J=6, 7Hz, 2H), 2.83-2.85(m, 2H), 2.76-2.80(m, 2H), 1.56-1.68(m, 4H), 1.38(s, 18H), 1.33-1.43(m, 2H), 1.04-1.30(m, 6H), 0.75-0.88(m, 3H)

IR (cm⁻¹) 3640, 3316, 2924, 1640, 1558, 1436, 1233, 749

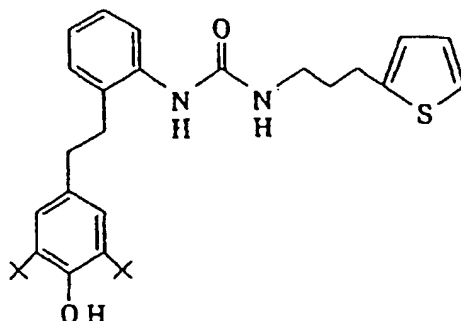
Example 9

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-[3-(2-thienyl)propyl]urea

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The title compound was prepared in a similar manner to that mentioned in Example 1, using 4-(2-thienyl)butanoic acid instead of 4-hexyloxybenzoic acid.

m.p. 150°C

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$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.19-7.27(m, 4H), 7.07(dd, $J=4$, 1Hz, 1H), 6.87(dd, $J=3$, 2Hz, 1H), 6.77(s, 2H), 6.71(t, $J=2\text{Hz}$, 1H), 5.11(s, 1H), 4.96(s, 1H), 4.21(t, 1H), 3.20(s, 2H), 2.77-2.87(m, 6H), 1.81(qui, $J=7\text{Hz}$, 2H), 1.37(s, 18H)
 IR (cm^{-1}) 3638, 3286, 2918, 1630, 1570, 1434, 1233, 696

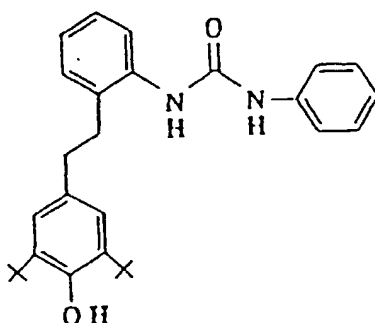
30 Example 10

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-phenylurea

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The title compound was prepared in a similar manner to that mentioned in Example 1, using benzoic acid instead of 4-hexyloxybenzoic acid. m.p. 207°C

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$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.22-7.36(m, 8H), 7.02(t, $J=7\text{Hz}$, 1H), 6.80(s, 2H), 6.02(s, 1H), 5.18(s, 1H), 5.15(s, 1H), 2.79-2.91(m, 4H), 1.38(s, 18H)
 IR (cm^{-1}) 3630, 3350, 2950, 1650, 1600, 1550, 1500, 1230, 750

Example 11

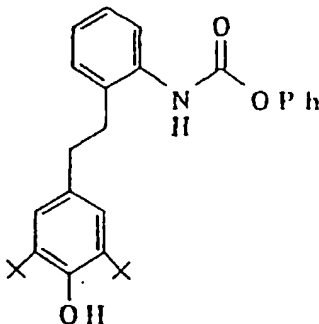
(1) N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]phenyl carbamate

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To a solution of 4-(2-aminophenethyl)-2,6-di-tert-butylphenol (7.00 g, 21.5 mmol) and diisopropylamine (3.4 ml, 24 mmol) in dichloromethane (50 ml) was added dropwise a solution of phenyl chloroformate (3.60 g, 23.0 mmol) in dichloromethane (10 ml) so that the internal temperature does not exceed 0°C over a ice-cold water bath. The mixture was stirred at the same temperature for 2 hrs, washed with water, dried over MgSO₄ and concentrated. Purification of the residue by a silica gel column chromatography gave a viscous oil of N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]phenyl carbamate (8.16 g, 85.2% yield).

¹H-NMR (δ ppm, CDCl₃) 7.63(bs, 1H), 7.34(t, J=8Hz, 2H), 7.08-7.29(m, 6H), 6.80(s, 2H), 5.74(bs, 1H), 5.13(s, 1H), 2.8-2.9(m, 4H), 1.35(s, 18H)

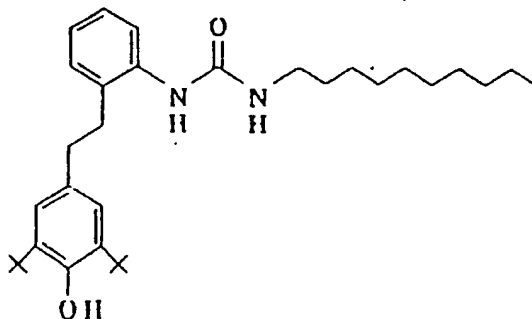
(2) N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-decylurea

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A solution of N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]phenyl carbamate (1.0 g, 2.2 mmol) and decylamine (0.38 g, 2.4 mmol) in xylene (10 ml) was heated under reflux for 2.5 hrs. After distilling off the solvent, purification of the residue by a silica gel column chromatography afforded waxy N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-decylurea (0.93 g, 85% yield).

¹H-NMR (δ ppm, CDCl₃) 7.17-7.26(m, 4H), 6.78(s, 2H), 5.11(s, 1H), 4.98(s, 1H), 4.17(t, J=6Hz, 1H), 3.09-3.16(m, 2H), 2.76-2.87(m, 4H), 1.50-2.50(m, 16H), 1.38(s, 18H), 0.87(t, J=7Hz, 3H)
IR (cm⁻¹) 3650, 3350, 2960, 2930, 2850, 1640, 1570

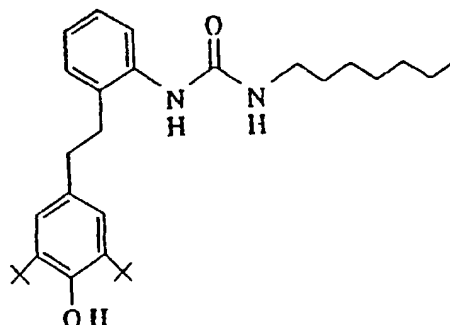
Example 12

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-heptylurea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using heptylamine instead of decylamine. m.p. 100°C

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$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.18-7.27(m, 4H), 6.78(s, 2H), 5.11(s, 1H), 4.99(s, 1H), 4.18(bt, $J=5\text{Hz}$, 1H), 2.89(q, $J=6\text{Hz}$, 2H), 2.79-2.85(m, 4H), 1.38-1.45(m, 2H), 1.38(s, 18H), 1.15-1.30(m, 8H), 0.86(t, $J=7\text{Hz}$, 3H)
 IR (cm^{-1}) 3650, 3320, 2970, 2940, 2870, 1640, 1570, 1440, 1240, 760

Example 13

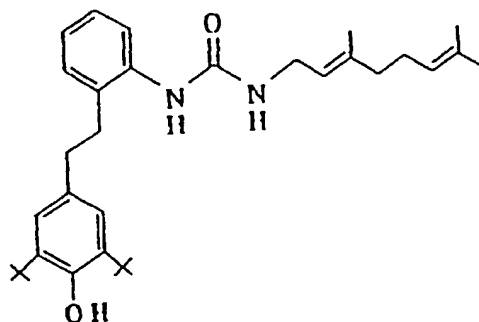
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N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(3,7-dimethyl-2,6-octadienyl)urea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 3,7-dimethyl-2,6-octadienylamine instead of decylamine. m.p. 87.0-87.5°C

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$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.16-7.30(m, 4H), 6.78(s, 2H), 5.10(s, 1H), 5.05-5.13(m, 1H), 5.02(bs, 2H), 4.05-4.12(m, 1H), 3.75(t, $J=6\text{Hz}$, 2H), 2.80-2.85(m, 2H), 2.75-2.80(m, 2H), 1.95-2.08(m, 2H), 1.89-1.95(m, 2H), 1.65(s, 3H), 1.60(s, 3H), 1.57(s, 3H), 1.37(s, 18H)
 IR (cm^{-1}) 3628, 3312, 2956, 1638, 1585, 1436, 1233, 752

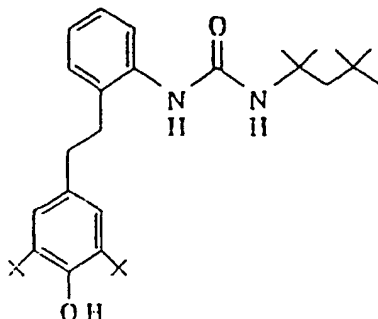
Example 14

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(2,4,4-trimethyl-2-pentyl)urea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 2,2,4-trimethyl-2-pentylamine instead of decylamine. m.p. 168-169°C

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¹H-NMR (δ ppm, CDCl₃) 7.15-7.26(m, 4H), 6.83(s, 2H), 5.09(s, 2H), 4.18(s, 1H), 2.71-2.87(m, 4H), 1.64(s, 2H), 1.39(s, 18H), 1.34(s, 6H), 0.90(s, 9H)

IR (cm⁻¹) 3640, 3334, 2956, 1645, 1556, 1437, 1365, 1226

Example 15

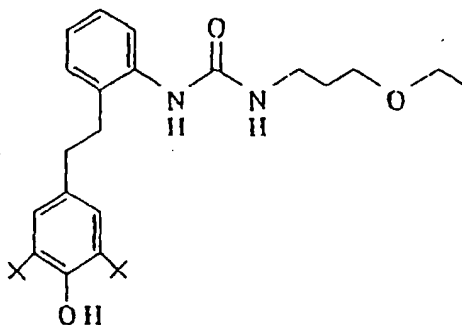
30

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(3-ethoxypropyl)urea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 3-ethoxypropylamine instead of decylamine. m.p. 136-137°C

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¹H-NMR (δ ppm, CDCl₃) 7.16-7.27(m, 4H), 6.79(s, 2H), 5.10(s, 1H), 5.06(s, 1H), 4.78(t, J=5Hz, 1H), 3.40(t, J=6Hz, 2H), 3.32(dd, J=14, 7Hz, 2H), 3.28(q, J=6Hz, 2H), 2.84-2.88(m, 2H), 2.77-2.80(m, 2H), 1.67-1.73(m, 2H), 1.38(s, 18H), 0.99(t, J=7Hz, 3H)

IR (cm⁻¹) 3600, 3346, 2952, 1638, 1563, 1436, 1288, 1238, 1108, 753

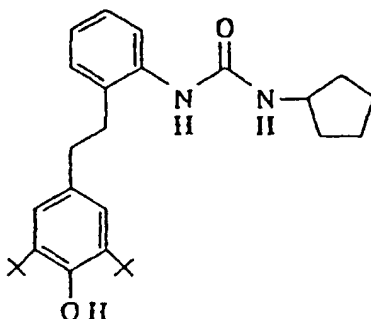
Example 16

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-cyclopentylurea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using cyclopentylamine instead of decylamine. m.p. 186-187°C

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$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.15-7.28(m, 4H), 6.79(s, 2H), 5.11(s, 1H), 5.08(s, 1H), 4.17(d, $J=7\text{Hz}$, 1H), 4.01-4.10(m, 1H), 2.76-2.87(m, 4H), 1.89-1.96(m, 2H), 1.50-1.61(m, 4H), 1.39(s, 18H), 1.22-1.29(m, 2H)
 IR (cm^{-1}) 3650, 3350, 2950, 1640, 1580, 1560, 1440, 1240

Example 17

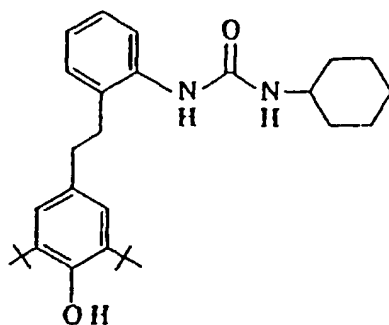
30

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-cyclohexylurea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using cyclohexylamine instead of decylamine. m.p. 198-200°C

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$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.16-7.25(m, 4H), 6.78(s, 2H), 5.14(s, 1H), 4.99(s, 1H), 4.09(d, $J=5\text{Hz}$, 1H), 3.59-3.62(m, 1H), 2.83(d, $J=6\text{Hz}$, 2H), 2.79(d, $J=6\text{Hz}$, 2H), 1.95-1.99(m, 2H), 1.53-1.64(m, 4H), 1.38(s, 18H), 1.26-1.30(m, 2H), 0.96-0.99(m, 2H)
 IR (cm^{-1}) 3290, 2930, 1630, 1561, 1232

Example 18

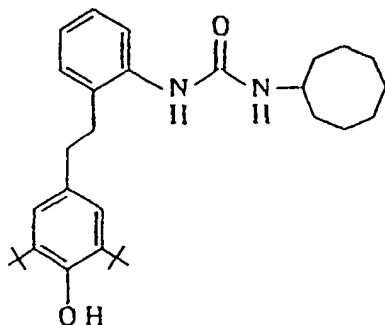
N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-cyclooctylurea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using cyclooctylamine instead of decylamine. m.p. 174-176°C

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$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.17-7.24(m, 4H), 6.79(s, 2H), 5.10(s, 1H), 5.05(s, 1H), 4.19(d, J=5Hz, 1H), 3.68-3.98(m, 1H), 2.83(d, J=6Hz, 2H), 2.79(d, J=6Hz, 2H), 1.74-1.81(m, 2H), 1.42-1.58(m, 12H), 1.38(s, 18H)
 IR (cm^{-1}) 3308, 2922, 1630, 1554, 1435, 1233

Example 19

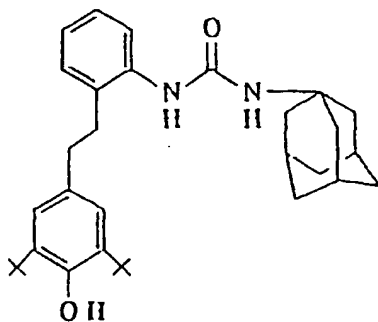
30

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-adamantylurea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 1-adamantanamine instead of decylamine. m.p. 197-199°C

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$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.14-7.29(m, 4H), 6.83(s, 2H), 5.11(s, 1H), 5.10(s, 1H), 4.06(s, 1H), 2.79-2.85(m, 4H), 1.91-2.05(m, 9H), 1.60-1.70(m, 6H), 1.39(s, 18H)
 IR (cm^{-1}) 3350, 2900, 2850, 1640, 1550, 1440, 1300, 1240

Example 20

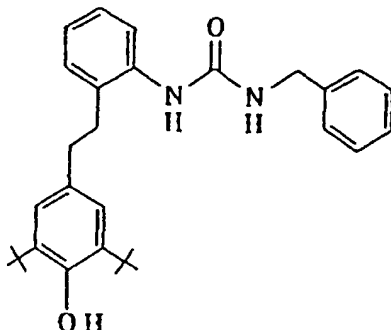
N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-benzylurea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using benzylamine instead of decylamine. m.p. 181-183°C

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¹H-NMR (δ ppm, CDCl₃) 7.15-7.30(m, 9H), 6.77(s, 2H), 5.13(s, 1H), 5.08(s, 1H), 4.54(t, J=6Hz, 1H), 4.33(d, J=6Hz, 2H), 2.82(d, J=6Hz, 2H), 2.78(d, J=6Hz, 2H), 1.35(s, 18H)
IR (cm⁻¹) 3294, 2956, 1629, 1579, 1435, 1233, 741

Example 21

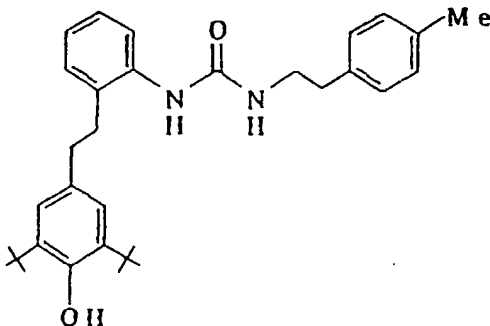
30

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(4-methylphenethyl)urea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 4-methylphenethylamine instead of decylamine.

m.p. 170-172°C

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¹H-NMR (δ ppm, CDCl₃) 7.12-7.23(m, 4H), 7.04(d, J=8Hz, 2H), 6.98(d, J=8Hz, 2H), 6.76(s, 2H), 5.09(s, 1H), 4.96(s, 1H), 4.22(t, J=6Hz, 1H), 3.36(q, J=6Hz, 2H), 2.80(d, J=6Hz, 2H), 2.69(t, J=6Hz, 2H), 2.68(d, J=6Hz, 2H), 2.29(s, 3H), 1.36(s, 18H)

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IR (cm⁻¹) 3342, 2950, 1643, 1563, 1435

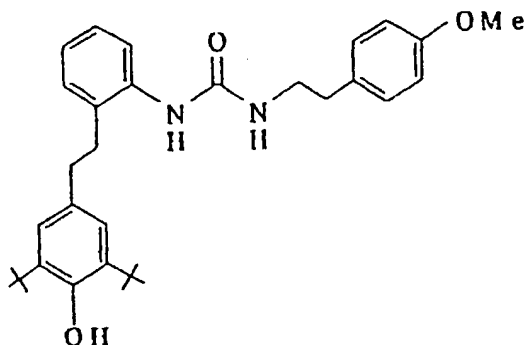
Example 22

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(4-methoxyphenethyl)urea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 4-methoxyphenethylamine instead of decylamine.

m.p. 148-149°C

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$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.10-7.24(m, 4H), 7.00(d, $J=9\text{Hz}$, 2H), 6.77(d, $J=9\text{Hz}$, 2H), 6.76(s, 2H), 5.09(s, 1H), 4.95(s, 1H), 4.20(t, $J=6\text{Hz}$, 1H), 3.76(s, 3H), 3.33(q, $J=6\text{Hz}$, 2H), 2.80(d, $J=6\text{Hz}$, 2H), 2.77(d, $J=6\text{Hz}$, 2H), 2.67(t, $J=6\text{Hz}$, 2H), 1.36(s, 18H)

IR (cm^{-1}) 3420, 2960, 1641, 1561, 1525, 1249

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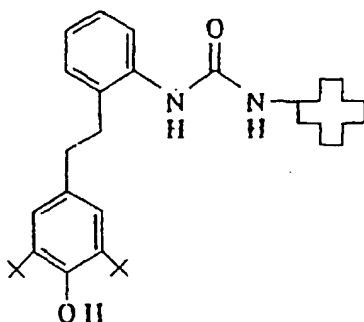
Example 23

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-cyclododecylurea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using cyclododecylamine instead of decylamine.

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$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.06-7.29(m, 4H), 6.80(s, 2H), 5.10(s, 2H), 4.05(d, $J=9\text{Hz}$, 1H), 3.89(s, 1H), 2.76-2.87(m, 4H), 1.38(s, 18H), 1.20-1.30(m, 22H)

IR (cm^{-1}) 3650, 3340, 2950, 2920, 1640, 1560, 1440, 1240

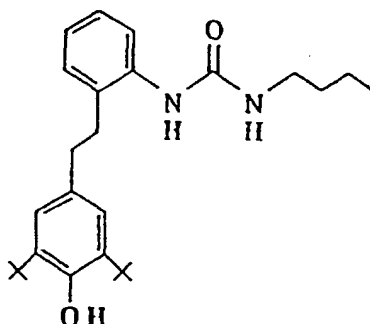
Example 24

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-butylurea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using butylamine instead of decylamine. m.p. 133-134°C

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$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.16-7.26(m, 4H), 6.78(s, 2H), 5.12(s, 1H), 4.97(s, 1H), 4.16(t, J=6Hz, 1H), 3.11-3.16(m, 2H), 2.77-2.87(m, 4H), 1.38(s, 18H), 1.21-1.34(m, 4H), 0.87(t, J=7Hz, 3H)
 IR (cm^{-1}) 3450, 3320, 2960, 1640, 1570, 1460, 1440, 1250, 1230

Example 25

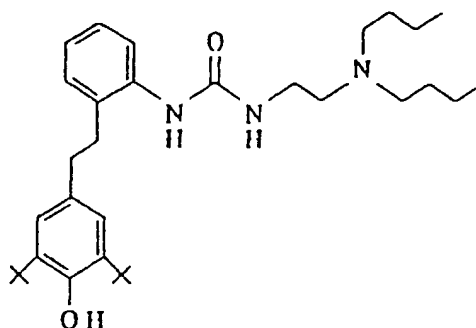
30

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-[2-(N,N-dibutylamino)ethyl]urea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using N,N-dibutylethylenediamine instead of decylamine.

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$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.18-7.26(m, 4H), 6.80(s, 2H), 5.18(s, 1H), 5.10(s, 1H), 5.02(bs, 1H), 3.17-3.21(m, 2H), 2.76-2.87(m, 4H), 2.40(t, J=6Hz, 2H), 2.24(t, J=7Hz, 4H), 1.38(s, 18H), 1.04-1.26(m, 8H), 0.82(t, J=7Hz, 6H)
 IR (cm^{-1}) 3650, 3360, 2960, 2880, 1640, 1560, 1440, 1240

Further, the hydrochloride of the title compound was prepared in the following manner.

Conc. hydrochloric acid (0.17 ml) was added to a solution of the title compound (0.95 g) in ethanol (12 ml). Distilling off the solvent afforded a waxy hydrochloride of the title compound (1.05 g).

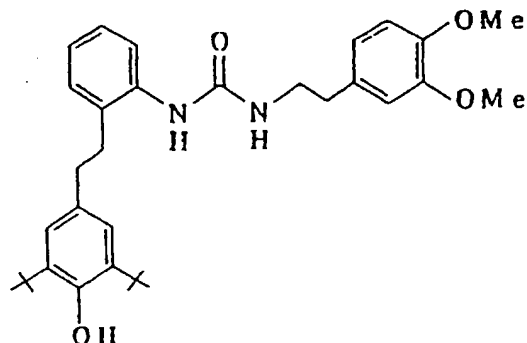
Example 26

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(3,4-dimethoxyphenethyl)urea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 3,4-dimethoxyphenethylamine instead of decylamine. m.p. 158-160°C

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$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.10-7.24(m, 4H), 6.76(s, 2H), 6.70-6.75(m, 1H), 6.60-6.65(m, 2H), 5.10(s, 1H), 5.00(s, 1H), 4.27(t, $J=6\text{Hz}$, 1H), 3.83(s, 3H), 3.81(s, 3H), 3.35-3.40(dt, $J=6, 7\text{Hz}$, 2H), 2.72-2.84(m, 4H), 2.68(t, $J=7\text{Hz}$, 2H), 1.36(s, 18H)
 IR (cm^{-1}) 3628, 3318, 1632, 1562, 1518, 1264, 1234

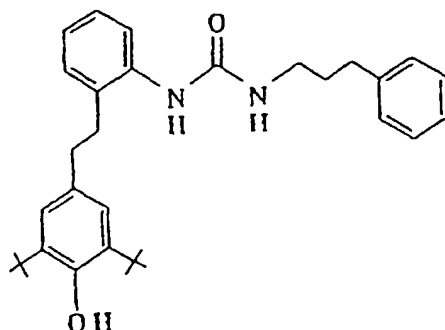
30 Example 27

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(3-phenylpropyl)urea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 3-phenylpropylamine instead of decylamine. m.p. 161-162°C

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$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.13-7.25(m, 7H), 7.10(d, $J=8\text{Hz}$, 2H), 6.77(s, 2H), 5.10(s, 1H), 4.98(s, 1H), 4.20(t, $J=7\text{Hz}$, 1H), 3.17(q, $J=7\text{Hz}$, 2H), 2.83(d, $J=6\text{Hz}$, 2H), 2.79(d, $J=6\text{Hz}$, 2H), 2.56(t, $J=7\text{Hz}$, 2H), 1.74(qui, $J=7\text{Hz}$, 2H), 1.36(s, 18H)
 IR (cm^{-1}) 3628, 3328, 2952, 1637, 1562, 1435, 1234, 748, 697

Example 28

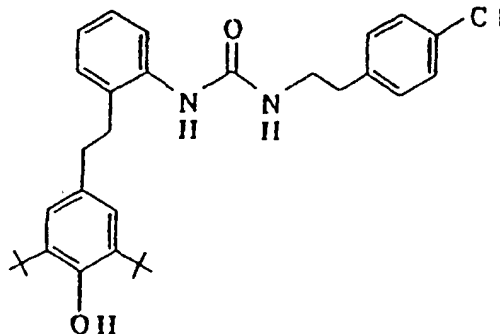
N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(4-chlorophenethyl)urea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 4-chlorophenethylamine instead of decylamine. m.p. 173-174°C

¹H-NMR (δ ppm, CDCl₃) 7.09-7.20(m, 6H), 7.02(d, 2H), 6.75(s, 2H), 5.10(s, 1H), 4.91(s, 1H), 4.16(t, J=6Hz, 1H), 3.35(q, J=6Hz, 2H), 2.78(q, J=5Hz, 4H), 2.70(t, J=7Hz, 2H), 1.35(s, 18H)
IR (cm⁻¹) 3626, 3322, 2950, 1638, 1561, 1493, 1436, 1234

Example 29

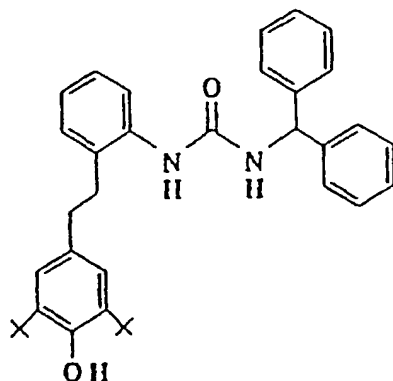
30

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-diphenylmethylurea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using benzhydramine instead of decylamine. m.p. 187.4°C

¹H-NMR (δ ppm, CDCl₃) 7.14-7.33(m, 14H), 6.75(s, 2H), 6.10(d, J=8Hz, 1H), 5.17(s, 1H), 5.08(s, 1H), 4.86(d, J=8Hz, 1H), 2.73-2.81(m, 4H), 1.35(s, 18H)
IR (cm⁻¹) 2960, 1640, 1560, 1500, 1460, 1440, 1240, 740, 700

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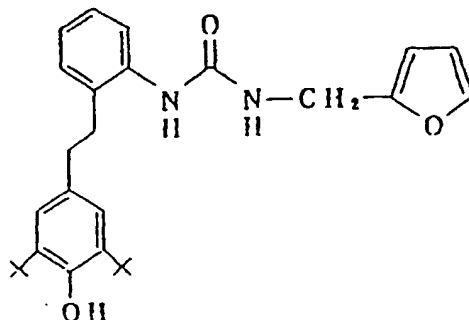
Example 30

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-[(2-furyl)methyl]urea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 2-aminomethylfuran instead of decylamine. m.p. 169.7°C

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¹H-NMR (δ ppm, CDCl₃) 7.15-7.28(m, 5H), 6.76(s, 2H), 6.26-6.27(m, 1H), 6.14-6.15(m, 1H), 5.10(s, 1H), 4.99(s, 1H), 4.45(t, J=6Hz, 1H), 4.32(d, J=6Hz, 2H), 2.76-2.86(m, 4H), 1.36(s, 18H)
IR (cm⁻¹) 3320, 2950, 1640, 1590, 1570, 1460, 1440, 1240, 730

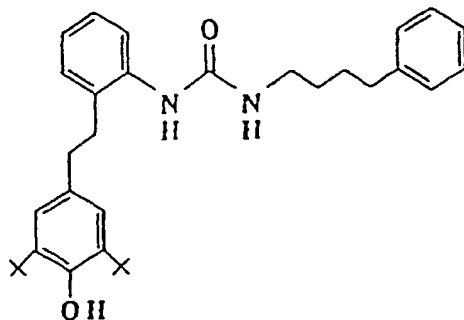
Example 31

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(4-phenylbutyl)urea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 4-phenylbutylamine instead of decylamine. m.p. 157.0°C

¹H-NMR (δ ppm, CDCl₃) 7.11-7.27(m, 9H), 6.77(s, 2H), 5.10(s, 1H), 4.95(s, 1H), 4.15(t, 1H), 3.12-3.17(m, 2H), 2.74-2.86(m, 4H), 2.58(t, J=8Hz, 2H), 1.39-1.61(m, 4H), 1.37(s, 18H)
IR (cm⁻¹) 3300, 2950, 2860, 1620, 1600, 1580, 1440, 1250, 1240

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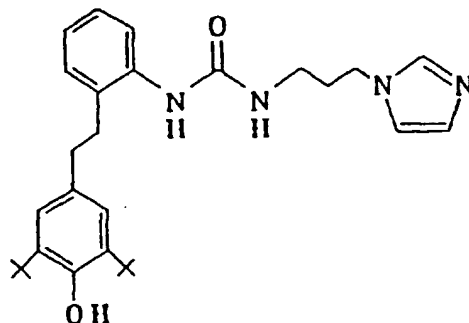
Example 32

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-[3-(1-imidazolyl)propyl]urea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using N-(3-aminopropyl)imidazole instead of decylamine.

m.p. 163.5°C

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$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.39(s, 1H), 7.20-7.29(m, 4H), 7.01(s, 1H), 6.85-6.86(m, 1H), 6.77(s, 2H), 5.15(s, 1H), 4.97(s, 1H), 4.25(t, J=6Hz, 1H), 3.92(t, J=7Hz, 2H), 3.13(dt, J=8, 7Hz, 2H), 2.77-2.86(m, 4H), 1.88-1.95(m, 2H), 1.37(s, 18H)

IR (cm^{-1}) 3360, 3320, 2960, 1640, 1570, 1520, 1440, 1240

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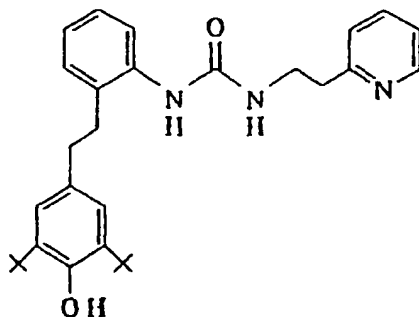
Example 33

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-[2-(2-pyridyl)ethyl]urea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 2-(2-aminoethyl)pyridine instead of decylamine.

m.p. 179.7°C

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$^1\text{H-NMR}$ (δ ppm, CDCl_3) 8.32(d, J=4Hz, 1H), 7.52-7.56(m, 1H), 7.06-7.27(m, 6H), 6.77(s, 2H), 5.21(t, J=6Hz, 1H), 5.11(s, 1H), 5.10(s, 1H), 3.56(q, J=6Hz, 2H), 2.93(t, J=6Hz, 2H), 2.67-2.83(m, 4H), 1.37(s, 18H)

IR (cm^{-1}) 3350, 2960, 1650, 1590, 1570, 1440, 760

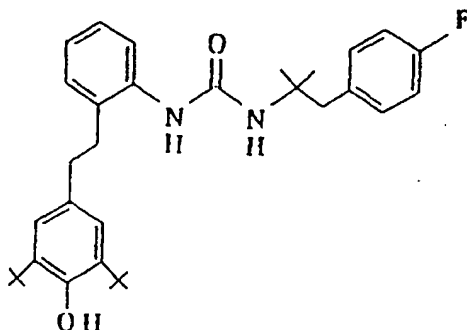
Example 34

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(1-(4-fluorophenyl)-2-methyl-2-propyl)urea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 4-fluoro- α,α dimethylphenethylamine instead of decylamine.
m.p. 150.6°C

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$^1\text{H-NMR}$ (δ ppm, CDCl_3) 6.84-7.26(m, 8H), 6.80(s, 2H), 5.10(s, 1H), 5.09(s, 1H), 3.95(s, 1H), 2.95(s, 2H), 2.72-2.82(m, 4H), 1.37(s, 18H), 1.25(s, 6H)
IR (cm^{-1}) 3350, 2960, 1640, 1560, 1510, 1440, 1240

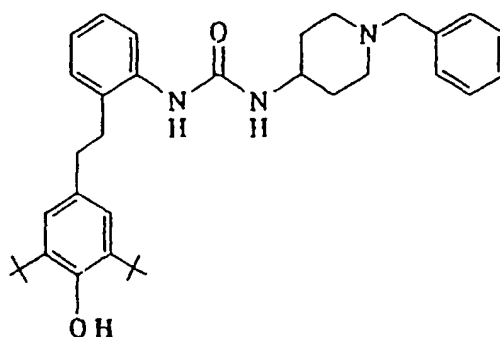
30 Example 35

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(1-benzyl-4-piperidyl)urea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 4-amino-1-benzylpiperidine instead of decylamine. m.p. 79-81°C

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$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.20-7.34(m, 9H), 6.77(s, 2H), 5.10(s, 1H), 4.99(s, 1H), 4.07-4.15(m, 1H), 3.58-3.72(m, 1H), 3.44(s, 2H), 2.68-2.86(m, 6H), 2.00-2.10(m, 2H), 1.80-1.90(m, 2H), 1.37(s, 18H), 1.24-1.35(m, 2H)
IR (cm^{-1}) 3632, 3350, 1640, 1552

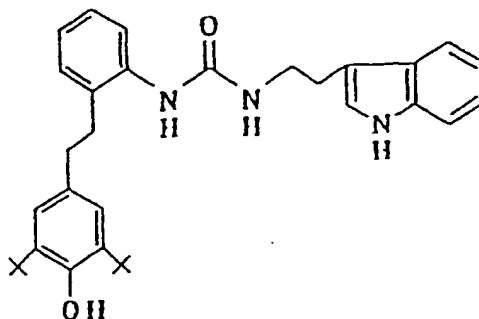
Example 36

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-[2-(3-indolyl)ethyl]urea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 3-(2-aminoethyl)indole instead of decylamine.

m.p. 193-194°C

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¹H-NMR (δ ppm, CDCl₃) 7.92(s, 1H), 7.54(d, J=8Hz, 1H), 7.33(d, J=8Hz, 1H), 7.05-7.26(m, 6H), 6.90(d, J=2Hz, 1H), 6.77(s, 2H), 5.10(s, 1H), 5.00(s, 1H), 4.32(t, J=6Hz, 1H), 3.47(dt, J=6, 7Hz, 2H), 2.90(t, J=7Hz, 2H), 2.73-2.81(m, 4H), 1.35(s, 18H)

IR (cm⁻¹) 3430, 3340, 2880, 1640, 1560, 1440, 1240, 750

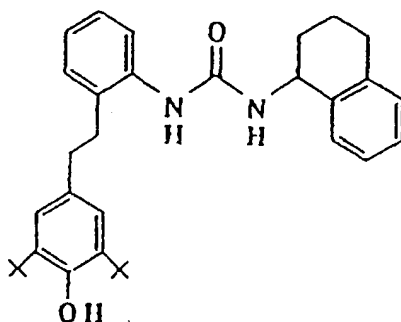
30 Example 37

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(1,2,3,4-tetrahydro-1-naphthyl)urea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 1,2,3,4-tetrahydro-1-naphthylamine instead of decylamine. m.p. 168-169°C

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¹H-NMR (δ ppm, CDCl₃) 7.01-7.27(m, 8H), 6.77(s, 2H), 5.08(s, 1H), 5.01-5.06(m, 2H), 4.42(d, J=8Hz, 1H), 2.65-2.90(m, 6H), 1.50-2.10(m, 4H), 1.35(s, 18H)

IR (cm⁻¹) 3650, 3350, 2960, 1640, 1560, 1440, 1240

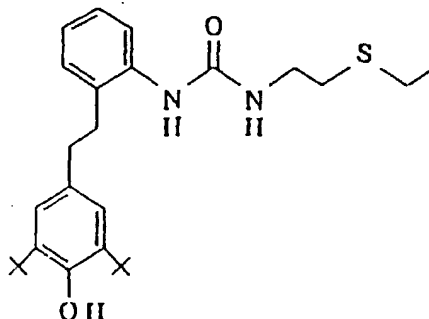
Example 38

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(2-ethylthioethyl)urea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 2-ethylthioethylamine instead of decylamine.

25 m.p. 131-132°C

$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.19-7.28(m, 4H), 6.78(s, 2H), 5.12(s, 1H), 5.03(s, 1H), 4.63(t, $J=6\text{Hz}$, 1H), 3.33(dt, $J=6, 7\text{Hz}$, 2H), 2.80-2.85(m, 4H), 2.60(t, $J=7\text{Hz}$, 2H), 2.48(q, $J=7\text{Hz}$, 2H), 1.38(s, 18H), 1.20(t, $J=7\text{Hz}$, 3H)
 IR (cm^{-1}) 3570, 3320, 2950, 2920, 1640, 1570, 1440, 1250, 1240

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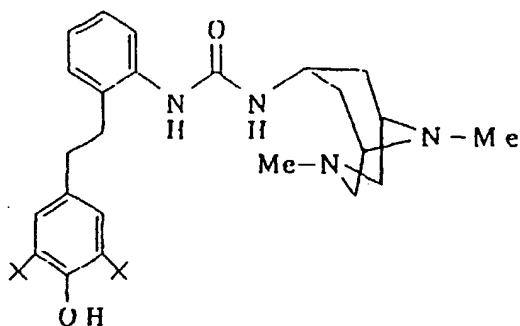
Example 39

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(3,9-dimethyl-3,9-diazabicyclo[3.3.1]nonyl)urea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 7-amino-3,9-dimethyl-3,9-diazabicyclo[3.3.1]nonane instead of decylamine.

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$^1\text{H-NMR}$ (δ ppm, CDCl_3) 8.55(d, $J=10\text{Hz}$, 1H), 7.14-7.27(m, 4H), 6.85(s, 2H), 5.14(s, 1H), 5.09(s, 1H), 4.10-4.26(m, 1H), 2.87-2.90(m, 2H), 2.77-2.80(m, 2H), 2.70(bs, 2H), 2.41(s, 3H), 2.19-2.38(m, 7H), 1.39(s, 18H), 1.23-1.37(m, 4H)
 IR (cm^{-1}) 3638, 2926, 1651, 1509, 1435, 1377, 733

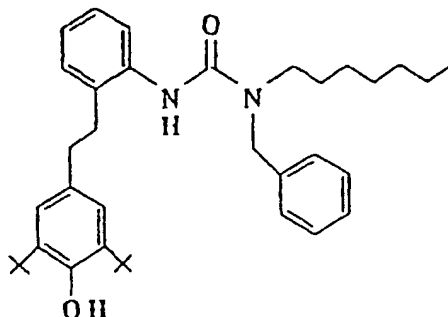
Example 40

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-benzyl-N'-heptylurea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using N-heptylbenzylamine instead of decylamine.

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$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.7-7.75(m, 1H), 6.9-7.3(m, 8H), 6.78(s, 2H), 5.96(s, 1H), 5.06(s, 1H), 4.49(s, 2H), 3.30(t, J=8Hz, 2H), 2.65-2.69(m, 2H), 2.51-2.54(m, 2H), 1.59-1.63(m, 2H), 1.38(s, 18H), 1.22-1.28(m, 8H), 0.86(t, J=7Hz, 3H)

IR (cm^{-1}) 3640, 2960, 2940, 2870, 1660, 1530, 1460, 1440, 1240, 760

Example 41

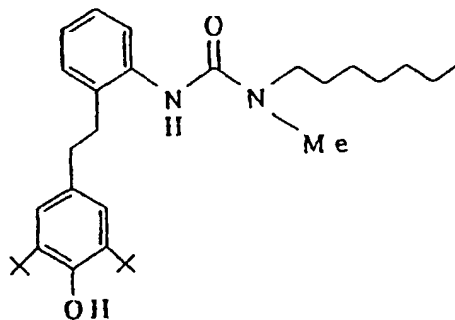
30

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-heptyl-N'-methylurea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using N-methylheptylamine instead of decylamine.

$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.36(d, J=8Hz, 1H), 7.18-7.22(m, 2H), 7.07-2.10(m, 1H), 6.81(s, 2H), 5.66(s, 1H), 5.08(s, 1H), 3.23(t, J=8Hz, 2H), 2.82(s, 4H), 2.71(s, 3H), 1.45-1.55(s, 2H), 1.36(s, 18H), 1.20-1.30(m, 8H), 0.86(t, J=7Hz, 3H)

IR (cm^{-1}) 2880, 2870, 2820, 1660, 1520, 1490, 1450, 1440, 1250, 760

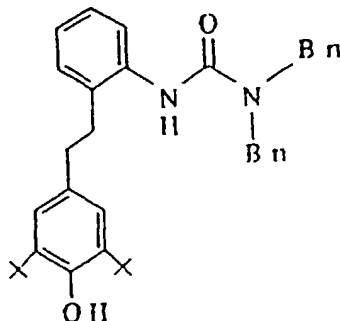
Example 42

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N',N'-dibenzylurea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using N,N-dibenzylamine instead of decylamine.

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$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.69(d, $J=8\text{Hz}$, 1H), 7.15-7.29(m, 10H), 7.00(m, 1H), 6.90(t, $J=8\text{Hz}$, 1H), 6.80(d, $J=8\text{Hz}$, 1H), 6.74(s, 2H), 6.01(bs, 1H), 5.05(s, 1H), 4.54(s, 4H), 2.59(t, $J=8\text{Hz}$, 2H), 2.38(t, $J=8\text{Hz}$, 2H), 1.37(s, 18H)
 IR (cm^{-1}) 3628, 3280, 2958, 1710, 1645, 1594, 1498, 1475, 1362, 1231, 754, 696

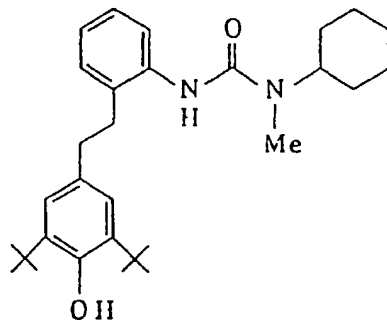
Example 43

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N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-cyclohexyl-N'-methylurea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using N-methylcyclohexylamine instead of decylamine. Amorphous powders.

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$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.65(d, $J=7\text{Hz}$, 1H), 7.15-7.21(m, 2H), 7.06(t, $J=7\text{Hz}$, 1H), 6.81(s, 2H), 5.68(bs, 1H), 5.08(s, 1H), 4.13(m, 1H), 2.82(s, 4H), 2.54(s, 3H), 1.75-1.81(m, 2H), 1.60-1.75(m, 3H), 1.25-1.40(m, 23H)
 IR (cm^{-1}) 3638, 3426, 2930, 1639, 1520, 1484, 1450, 1314, 1249, 1166, 1121, 751

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Example 44

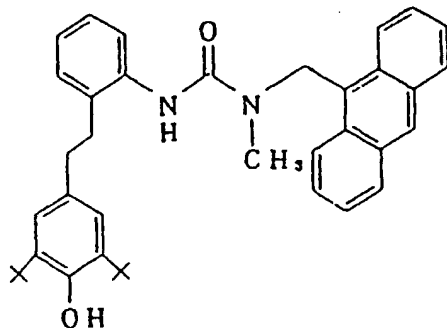
N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(9-anthryl)methyl-N'-methylurea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 9-(methylaminomethyl)anthracene instead of decylamine.
m.p. 205-206°C

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$^1\text{H-NMR}$ (δ ppm, CDCl_3) 8.47(s, 1H), 8.37(d, $J=9\text{Hz}$, 2H), 8.02-8.04(m, 2H), 7.70(d, $J=8\text{Hz}$, 1H), 7.43-7.57(m, 4H), 7.15-7.31(m, 3H), 6.67(s, 2H), 5.67(s, 1H), 5.59(s, 2H), 4.94(s, 1H), 2.76-2.86(m, 4H), 2.34(s, 3H), 1.19(s, 18H)
IR (cm^{-1}) 3420, 2950, 1640, 1520, 1490, 1450, 1440, 1250, 740

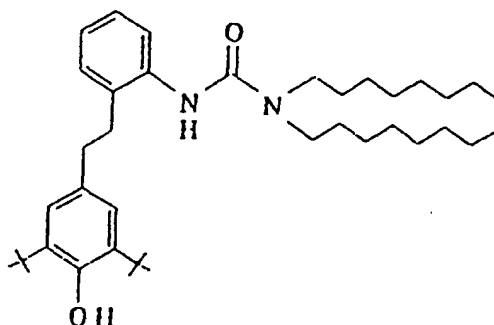
30 Example 45

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N',N'-dioctylurea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using N,N-dioctylamine instead of decylamine. m.p. 55-60°C

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$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.73(dd, $J=8$, 1Hz, 1H), 7.13-7.25(m, 2H), 7.00-7.05(m, 1H), 6.85(s, 2H), 5.94(s, 1H), 5.07(s, 1H), 3.18(t, $J=8\text{Hz}$, 4H), 2.81(s, 4H), 1.51-1.61(m, 4H), 1.39(s, 18H), 1.20-1.34(m, 20H), 0.87(t, $J=7\text{Hz}$, 6H)
IR (cm^{-1}) 3646, 3420, 3322, 1626, 1511

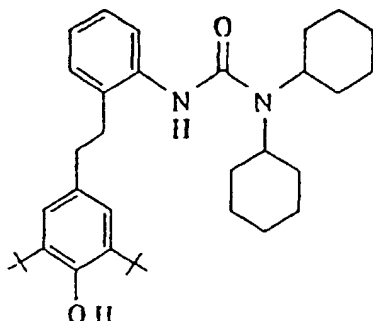
Example 46

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N',N'-dicyclohexylurea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using N,N-dicyclohexylamine instead of decylamine.

m.p. 149-152°C

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$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.73(dd, $J=8$, 1Hz, 1H), 7.15-7.20(m, 1H), 7.13(dd, $J=7$, 2Hz, 1H), 7.00-7.05(m, 1H), 6.94(s, 2H), 6.15(s, 1H), 5.06(s, 1H), 3.42-3.52(m, 2H), 2.84(s, 4H), 1.55-1.83(m, 14H), 1.41(s, 18H), 1.22-1.34(m, 4H), 0.98-1.13(m, 2H)

IR (cm^{-1}) 3474, 3400, 1644, 1588, 1517

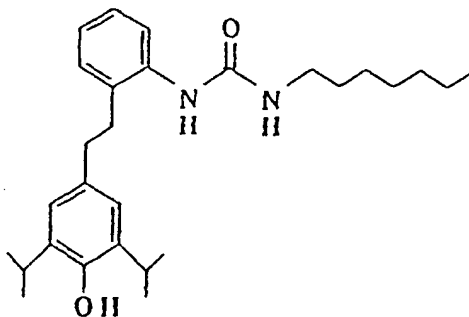
30 Example 47

N-[2-(3,5-diisopropyl-4-hydroxyphenethyl)phenyl]-N'-heptylurea

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A solution of diphenylphosphoryl azide (0.88 g, 3.2 mmol), octanoic acid (0.42 g, 2.9 mmol) and triethylamine (0.32 g, 3.2 mmol) in toluene (10 ml) was stirred at room temperature for 1.5 hrs and further stirred at about 90°C for 2 hrs. After allowing the mixture to cool, a solution of 4-(2-aminophenethyl)-2,6-diisopropylphenol (0.85 g, 2.9 mmol) in toluene (2 ml) was added dropwise under ice-cooling while stirring. The reaction solution was returned slowly to room temperature and stirred overnight. The solvent was distilled off, the residue was purified by a silica gel column chromatography and recrystallized from ethyl acetate/hexane to give crystals of the title compound (0.99 g, 76%). m.p. 150-151°C

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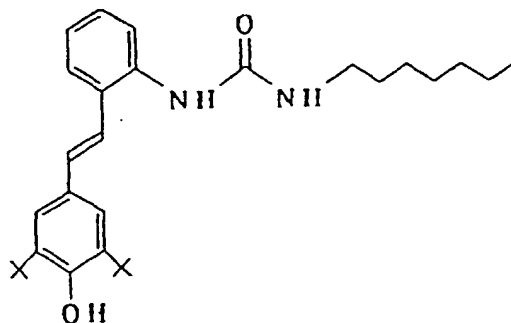
$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.16-7.26(m, 4H), 6.69(s, 2H), 5.14(s, 1H), 4.73(s, 1H), 4.18(t, $J=6\text{Hz}$, 1H), 3.01-3.15(m,

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4H), 2.71-2.89(m, 4H), 1.34-1.44(m, 2H), 1.2-1.3(m, 8H), 1.20,(s, 6H), 1.19(s, 6H), 0.86(t, J=7Hz, 3H)
 IR (cm⁻¹) 3330, 2960, 2930, 1640, 1580, 1470, 1450, 1260, 750

Example 48

N-[2-(3,5-di-tert-butyl-4-hydroxystyryl)phenyl]-N'-heptylurea



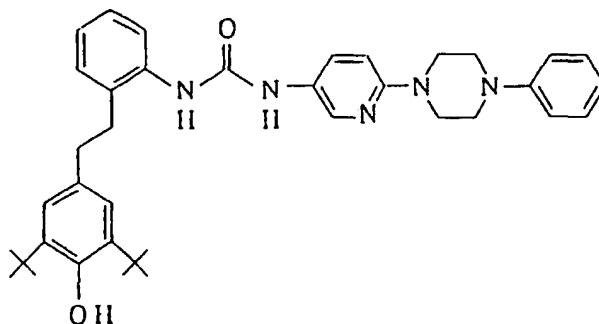
A solution of diphenylphosphoryl azide (0.36 g, 1.3 mmol), octanoic acid (0.17 g, 1.2 mmol) and triethylamine (0.13 g, 1.3 mmol) in toluene (5 ml) was stirred at room temperature for 1.5 hrs and further stirred at about 90°C for 2 hrs. After allowing the mixture to cool, a solution of 4-(2-aminostyryl)-2,6-di-tert-butylphenol (0.89 g, 1.2 mmol) in toluene (2 ml) was added dropwise under ice-cooling while stirring. The reaction solution was returned slowly to room temperature and stirred overnight. The solvent was distilled off, the residue was purified by a silica gel column chromatography and recrystallized from ethyl acetate/hexane to give crystals of the title compound (0.39 g, 70%). m.p. 162-164°C

¹H-NMR(δ ppm, CDCl₃) 7.63(dd, J=7, 2Hz, 1H), 7.33-7.37(m, 3H), 7.21-7.28(m, 2H), 7.08(d, J=16Hz, 1H), 7.01(d, J=16Hz, 1H), 6.01(bs, 1H), 5.33(s, 1H), 4.54(t, J=6Hz, 1H), 3.20(dt, J=6, 7Hz, 2H), 1.42-1.47(m, 20H), 1.20-1.36(m, 8H), 0.83(t, J=7Hz, 3H)

IR (cm⁻¹) 3626, 3334, 2954, 2926, 1642, 1568, 1454, 1439, 1235, 1152, 960, 751

Example 49

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-[2-(4-phenyl-1-piperadiny)-5-pyridyl]urea



The title compound was prepared in a similar manner to that mentioned in Example 1, using 6-(4-phenyl-1-piperadiny)nicotinic acid instead of 4-hexyloxybenzoic acid. m.p. 197-199°C

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¹H-NMR(δ ppm, CDCl₃) 7.95(d, J=2Hz, 1H), 7.67(dd, J=9, 2Hz, 1H), 7.39(d, J=9Hz, 1H), 7.17-7.33(m, 5H), 6.94-7.00(m, 2H), 6.89(dd, J=7, 7Hz, 1H), 6.81(s, 2H), 6.65(d, J=9Hz, 1H), 5.85(bs, 1H), 5.22(bs, 1H), 5.16(s, 1H), 3.62(t, J=5Hz, 4H), 3.28(t, J=5Hz, 4H), 2.76-2.92(m, 4H), 1.38(s, 18H)
 IR(cm⁻¹) 3620, 3330, 3290, 2954, 1646, 1600, 1547, 1492, 1233, 951, 760

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Example 50

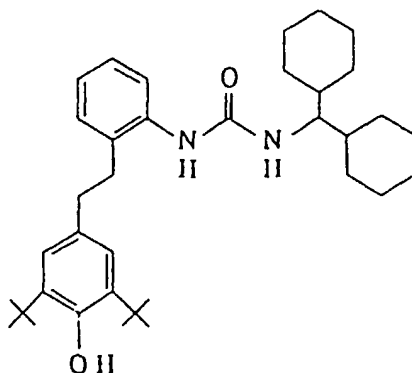
N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(dicyclohexylmethyl)urea

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The title compound was prepared in a similar manner to that mentioned in Example 1, using dicyclohexylacetic acid instead of 4-hexyloxybenzoic acid.
 m.p. 194-195°C

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¹H-NMR(δ ppm, CDCl₃) 7.29-7.18(m, 4H), 6.81(s, 2H), 5.19(bs, 1H), 5.09(s, 1H), 4.00(d, J=10Hz, 1H), 3.47(bs, 1H), 2.88(t, J=7Hz, 2H), 2.80(t, J=7Hz, 2H), 1.54-1.70(m, 10H), 1.38(s, 18H), 1.38-1.42(m, 2H), 1.01-1.19(m, 8H), 0.73-0.80(m, 2H)
 IR(cm⁻¹) 3642, 3362, 2924, 2852, 1641, 1553, 1436, 1235, 744

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Example 51

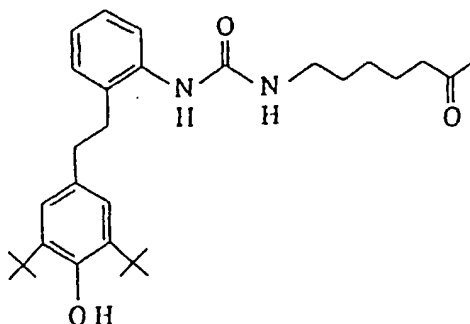
N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(6-oxoheptyl)urea

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The title compound was prepared in a similar manner to that mentioned in Example 1, using 7-oxooctanoic acid instead of 4-hexyloxybenzoic acid. m.p. 73-76°C

EP 0 625 507 B1

$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.16-7.25(m, 4H), 6.77(s, 2H), 5.12(s, 1H), 4.97(s, 1H), 4.17-4.24(m, 1H), 3.12(td, J=7, 6Hz, 2H), 2.76-2.86(m, 4H), 2.38(t, J=7Hz, 2H), 2.10(s, 3H), 1.49-1.57(m, 2H), 1.33-1.45(m, 4H), 1.37(s, 18H)
IR(cm^{-1}) 3368, 2950, 1712, 1632, 1574

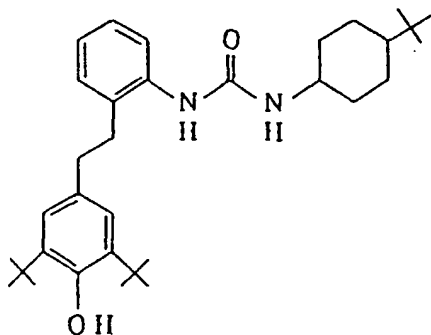
5 Example 52

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(4-tert-butylcyclohexyl)urea

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The title compound was prepared in a similar manner to that mentioned in Example 1, using 4-tert-butylcyclohexanecarboxylic acid instead of 4-hexyloxybenzoic acid. m.p. 206-208°C

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$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.15-7.25(m, 4H), 6.78(s, 2H), 5.10(s, 1H), 5.00(s, 1H), 4.02(d, J=8Hz, 1H), 3.47-3.57(m, 1H), 2.76-2.86(m, 4H), 1.96-1.98(m, 2H), 1.70-1.73(m, 2H), 1.38(s, 18H), 0.84-1.13(m, 5H), 0.81(s, 9H)
IR(cm^{-1}) 3642, 3356, 2948, 1640, 1585, 1436, 1234

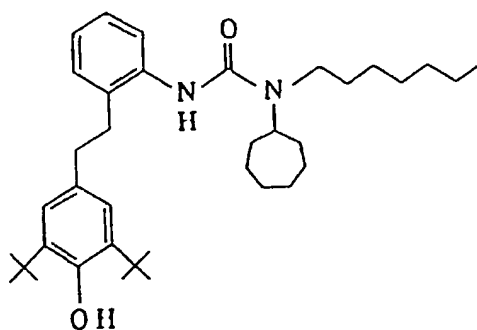
Example 53

35 N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-cycloheptyl-N'-heptylurea

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55 The title compound was prepared in a similar manner to that mentioned in Example 11, using N-heptylcycloheptylamine instead of decylamine. m.p. 70-72°C

$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.77(dd, J=8, 1Hz, 1H), 7.20(ddd, J=8, 8, 2Hz, 1H), 7.13(dd, J=8, 1Hz, 1H), 7.02(ddd, J=8, 8, 1Hz, 1H), 6.89(s, 2H), 6.04(s, 1H), 5.06(s, 1H), 4.02(bs, 1H), 3.07-3.11(m, 2H), 2.82(s, 4H), 1.82-1.87(m, 2H), 1.58-1.70(m, 8H), 1.40-1.56(m, 4H), 1.40(s, 18H), 1.25(bs, 8H), 0.84-0.90(m, 3H)

IR(cm^{-1}) 3642, 3296, 2910, 1631, 1588, 1435, 1235, 751

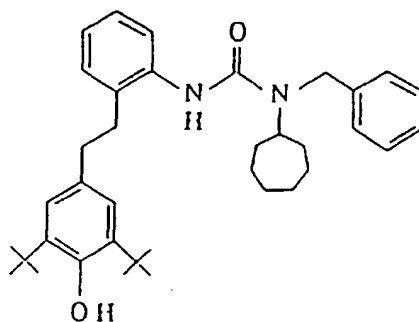
Example 54

5 N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-benzyl-N'-cycloheptylurea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using benzylcycloheptylamine instead of decylamine. m.p. 183-184°C

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$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.74(d, $J=8\text{Hz}$, 1H), 7.25-7.30(m, 2H), 7.07-7.21(m, 4H), 6.90-6.93(m, 2H), 6.76(s, 2H), 5.95(s, 1H), 5.06(s, 1H), 4.42-4.50(m, 1H), 4.43(s, 2H), 2.52(t, $J=8\text{Hz}$, 2H), 2.23(t, $J=8\text{Hz}$, 2H), 1.92-1.99(m, 2H), 1.43-1.72(s, 10H), 1.42(s, 18H)

IR(cm^{-1}) 3638, 3402, 2926, 1671, 1589, 1527, 1455, 1232, 1213, 752

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Example 55

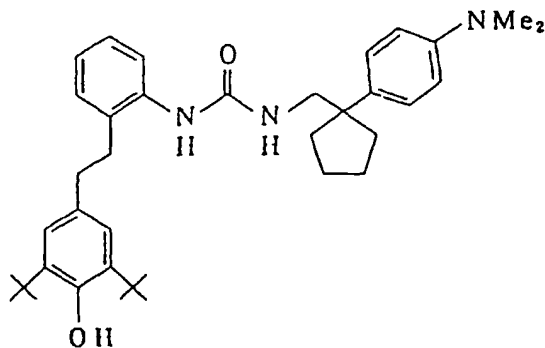
N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-[[1-(4-dimethylaminophenyl)cyclopentyl]methyl]urea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 4-[1-(aminomethyl)cyclopentyl]-N,N-dimethylaniline instead of decylamine. m.p. 174-175°C

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$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.08-7.21(m, 3H), 7.03(d, $J=7\text{Hz}$, 1H), 6.92(d, $J=9\text{Hz}$, 2H), 6.77(s, 2H), 6.54(d, $J=8\text{Hz}$, 2H), 5.07(s, 2H), 4.07-4.15(m, 1H), 3.22(d, $J=5\text{Hz}$, 2H), 2.88(s, 6H), 2.69-2.79(m, 4H), 1.63-1.83(m, 8H), 1.36(s, 18H)

IR(cm^{-1}) 3640, 3360, 1644, 1525, 1435, 1233, 814, 749

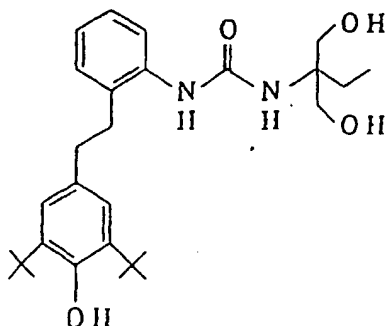
Example 56

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(2-ethyl-1,3-dihydroxy-2-propyl)urea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 2-amino-2-ethyl-1,3-propanediol instead of decylamine. m.p. 145-146°C

¹H-NMR(δ ppm, CDCl₃) 7.16-7.31(m, 4H), 6.78(s, 2H), 5.12(s, 1H), 5.11(s, 1H), 4.61(s, 1H), 3.75-3.89(m, 4H), 3.46-3.55(m, 2H), 2.75-2.88(m, 4H), 1.51(q, J=8Hz, 2H), 1.38(s, 18H), 0.75(t, J=8Hz, 3H)
IR(cm⁻¹) 3640, 3570, 3400, 3340, 2970, 1660, 1610, 1560, 1440, 1250, 750, 650

Example 57

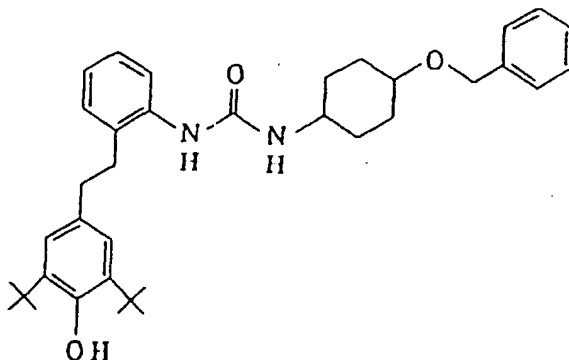
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N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(4-benzyloxycyclopropyl)urea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 4-benzyloxycyclohexylamine instead of decylamine.
m.p. 152-153°C

¹H-NMR(δ ppm, CDCl₃) 7.16-7.36(m, 9H), 6.77(s, 2H), 5.11(s, 1H), 4.94(s, 1H), 4.51(s, 2H), 4.00(d, J=8Hz, 1H), 3.56-3.68(m, 1H), 3.18-3.28(m, 1H), 2.74-2.86(m, 4H), 1.93-2.15(m, 4H), 1.31-1.47(m, 2H), 1.38(s, 18H), 0.94-1.08(m, 2H)
IR(cm⁻¹) 3630, 3370, 3330, 2950, 1645, 1565, 1235, 1090, 750

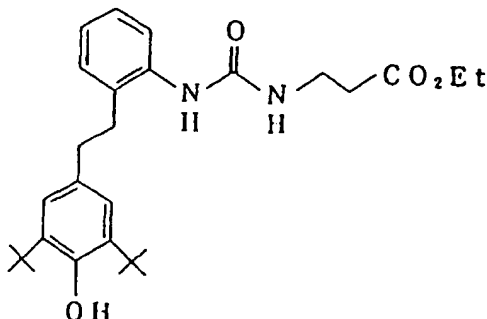
Example 58

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(2-ethoxycarbonyl)ethyl)urea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using ethyl 3-aminopropionate instead of decylamine. m.p. 158-159°C

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¹H-NMR(δ ppm, CDCl₃) 7.14-7.28(m, 4H), 6.78(s, 2H), 5.12(s, 1H), 5.08(s, 1H), 4.75(t, J=6Hz, 1H), 4.07(q, J=7Hz, 2H), 3.41(dt, J=6, 6Hz, 1H), 2.74-2.86(m, 4H), 2.49(t, J=6Hz, 2H), 1.38(18H.s, 18H), 1.18(t, J=7Hz, 3H)
IR(cm⁻¹) 3630, 3320, 3270, 2960, 1730, 1630, 1570, 1440, 1235, 1190, 745

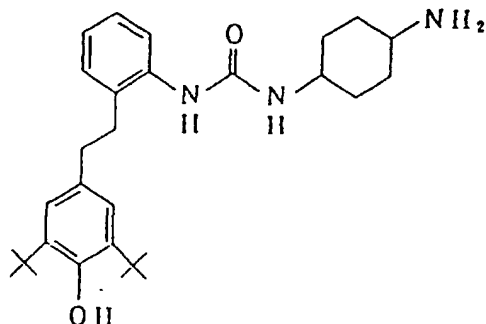
Example 59

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(4-aminocyclohexyl)urea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 1,4-diaminocyclohexane instead of decylamine.
m.p. >280°C (dec.)

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¹H-NMR(δ ppm, CDCl₃) 7.14-7.28(m, 4H), 6.77(s, 2H), 5.12(bs, 1H), 4.97(bs, 1H), 3.98-4.05(m, 1H), 3.53-3.64(m, 1H), 2.74-2.87(m, 4H), 2.52-2.62(m, 1H), 1.89-1.97(m, 2H), 1.77-1.86(m, 2H), 1.38(s, 18H), 0.97-1.24(m, 4H)
IR(cm⁻¹) 3630, 3420, 3340, 2940, 1635, 1590, 1570, 1240, 935

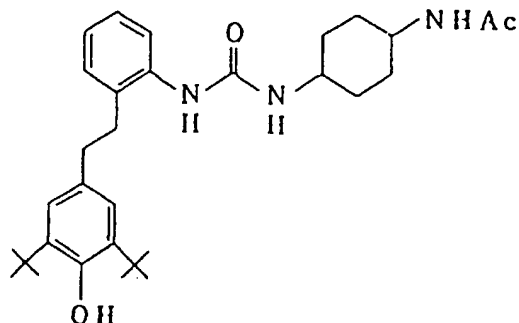
Example 60

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(4-acetamidocyclohexyl)urea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using N-(4-aminocyclohexyl)acetamide instead of decylamine.

m.p. 250°C (dec.)

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$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.16-7.30(m, 4H), 6.77(s, 2H), 5.26(bd, $J=8\text{Hz}$, 1H), 5.11(s, 1H), 4.93(s, 1H), 4.05(d, $J=8\text{Hz}$, 1H), 3.54-3.73(m, 2H), 2.74-2.87(m, 4H), 1.92-2.00(m, 4H), 1.93(s, 3H), 1.37(s, 18H), 1.03-1.27(m, 4H)
 $\text{IR}(\text{cm}^{-1})$ 3640, 3290, 2950, 1635, 1550, 1440, 1235, 760

Example 61

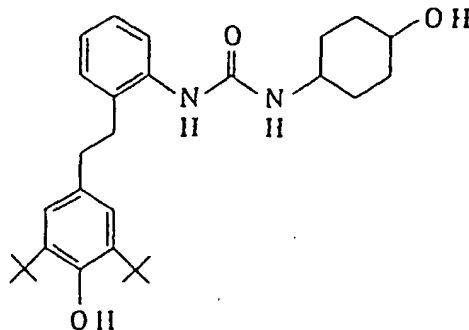
30

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(4-hydroxycyclohexyl)urea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 4-aminocyclohexanol instead of decylamine. m.p. 202-203°C

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$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.17-7.29(m, 4H), 6.77(s, 2H), 5.12(s, 1H), 4.94(s, 1H), 3.99(d, $J=8\text{Hz}$, 1H), 3.43-3.69(m, 2H), 2.75-2.87(m, 4H), 1.87-2.01(m, 4H), 1.28-1.43(m, 2H), 1.38(s, 18H), 0.97-1.12(m, 2H)
 $\text{IR}(\text{cm}^{-1})$ 3645, 3320, 2950, 1640, 1570, 1440, 1235, 1070, 880, 745

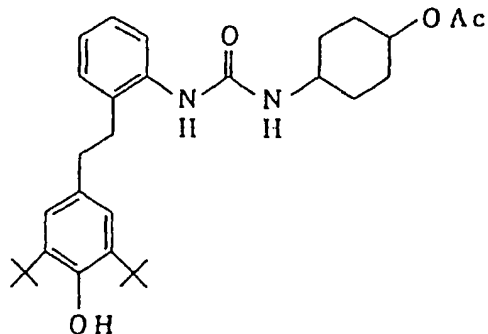
Example 62

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(4-acetoxycyclohexyl)urea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 4-aminocyclohexyl acetate instead of decylamine. m.p. 92-94°C

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$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.17-7.28(m, 4H), 6.77(s, 2H), 5.12(s, 1H), 4.93(s, 1H), 4.53-4.64(m, 1H), 4.02(d, J=8Hz, 1H), 3.57-3.71(m, 1H), 2.78-2.87(m, 4H), 2.01(s, 3H), 1.87-2.02(m, 4H), 1.32-1.52(m, 2H), 1.38(s, 18H), 1.02-1.16(m, 2H)

IR(cm^{-1}) 3640, 3380, 2960, 1740, 1645, 1560, 1440, 1245, 1050, 765

Example 63

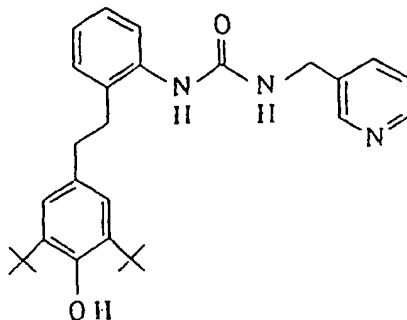
30

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(3-pyridylmethyl)urea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 3-(aminomethyl)pyridine instead of decylamine. m.p. 163-164°C

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$^1\text{H-NMR}$ (δ ppm, CDCl_3) 8.48(dd, J=5, 1Hz, 1H), 8.45(d, J=2Hz, 1H), 7.58(d, J=8Hz, 1H), 7.18-7.27(m, 5H), 6.75(s, 2H), 5.12(s, 1H), 4.95(s, 1H), 4.45-4.50(m, 1H), 4.34(d, J=6Hz, 2H), 2.75-2.86(m, 4H), 1.35(s, 18H)

IR(cm^{-1}) 3294, 1634, 1574, 1430, 1239, 1119, 760, 712

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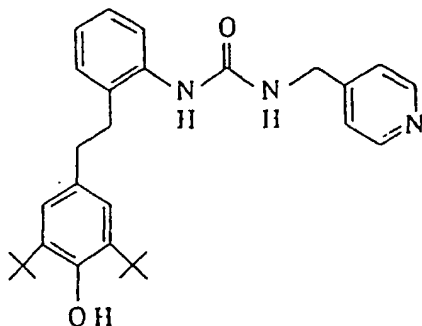
Example 64

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(4-pyridylmethyl)urea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 4-(aminomethyl)pyridine instead of decylamine. m.p. 214-215°C

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¹H-NMR(δ ppm, CDCl₃) 8.50(dd, J=4, 1Hz, 2H), 7.30-7.25(m, 2H), 7.20-7.24(m, 2H), 7.12(d, J=6Hz, 2H), 6.77(s, 2H), 5.13(s, 1H), 5.00(s, 1H), 4.54(t, J=6Hz, 1H), 4.34(d, J=6Hz, 2H), 2.86-2.90(m, 2H), 2.79-2.82(m, 2H), 1.35(s, 18H)

IR(cm⁻¹) 3292, 1632, 1573, 1436, 1237, 761

Example 65

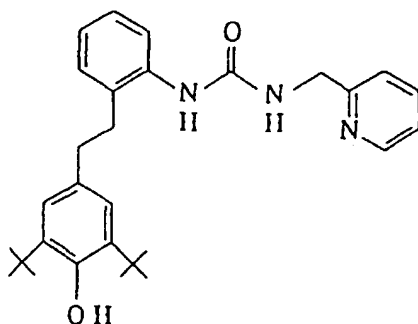
30

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(2-pyridylmethyl)urea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 2-(aminomethyl)pyridine instead of decylamine. m.p. 189-190°C

¹H-NMR(δ ppm, CDCl₃) 8.42(dd, J=4, 1Hz, 1H), 7.61(ddd, J=8, 8, 2Hz, 1H), 7.38(dd, J=8, 1Hz, 1H), 7.12-7.24(m, 5H), 6.80(s, 2H), 5.48(bs, 1H), 5.36(t, J=5Hz, 1H), 5.29(s, 1H), 4.47(d, J=6Hz, 2H), 2.78-2.89(m, 4H), 1.36(s, 18H)

IR(cm⁻¹) 3632, 3612, 3296, 1627, 1576, 1437, 1234, 755

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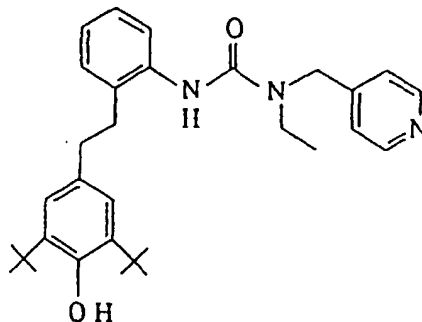
Example 66

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-ethyl-N'-(4-pyridylmethyl)urea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 4-(ethylaminomethyl)pyridine instead of decylamine.

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$^1\text{H-NMR}$ (δ ppm, CDCl_3) 8.51(dd, $J=4$, 1Hz, 2H), 7.66(dd, $J=8$, 1Hz, 1H), 7.09-7.25(m, 5H), 6.79(s, 2H), 5.85(s, 1H), 5.09(s, 1H), 4.50(s, 2H), 3.09(q, $J=7\text{Hz}$, 2H), 2.74-2.82(m, 4H), 1.36(s, 18H), 1.14(t, $J=7\text{Hz}$, 3H)
 IR(cm^{-1}) 3266, 3060, 1630, 1606, 1516, 1492, 1451, 1431, 1269, 755, 746

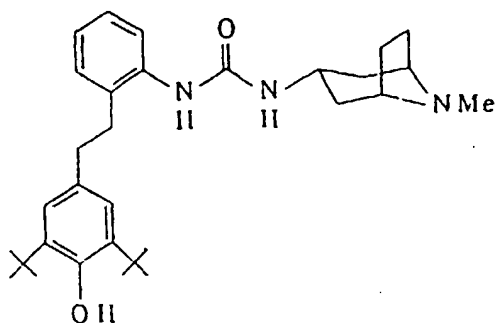
Example 67

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(8-methyl-8-azabicyclo[3.2.1]-3-octyl)urea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 3-amino-8-methyl-8-azabicyclo[3.2.1]octane instead of decylamine.

m.p. 229-230°C

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$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.27(d, $J=4\text{Hz}$, 1H), 7.13-7.21(m, 3H), 6.79(s, 2H), 5.51(bs, 1H), 5.14(s, 1H), 4.77(bs, 1H), 4.07-4.13(m, 1H), 3.51(bs, 2H), 2.76-2.87(m, 4H), 2.51(s, 3H), 2.13-2.15(m, 2H), 1.89-1.96(m, 6H), 1.38(m, 18H)
 IR(cm^{-1}) 3360, 1645, 1565, 1435, 1240, 745

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Example 68

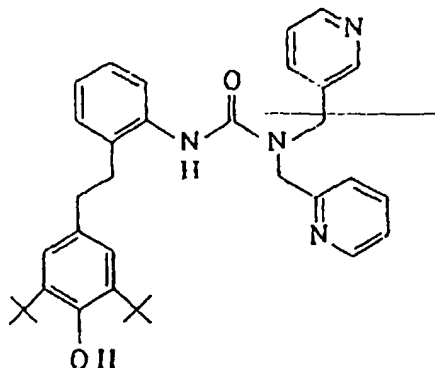
N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(2-pyridylmethyl)-N'-(3-pyridylmethyl)urea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using N-(3-pyridylmethyl)-2-pyridylmethylamine instead of decylamine.

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$^1\text{H-NMR}$ (δ ppm, CDCl_3) 9.47(s, 2H), 8.52(d, J=4Hz, 1H), 8.48(dd, J=5, 1Hz, 1H), 7.89(d, J=6Hz, 1H), 7.76(dd, J=8, 1Hz, 1H), 7.67(ddd, J=8, 8, 2Hz, 1H), 7.54(dd, J=8, 2Hz, 1H), 7.23(t, J=7Hz, 2H), 7.14-7.18(m, 1H), 7.02-7.06(m, 2H), 6.97(d, J=8Hz, 1H), 6.93(s, 2H), 5.19(s, 1H), 4.60(s, 2H), 4.37(s, 2H), 2.96-3.05(m, 2H), 2.90-2.94(m, 2H), 1.35(s, 18H)

$\text{IR}(\text{cm}^{-1})$ 3632, 3250, 1661, 1591, 1533, 1480, 1436, 1393, 1362, 1295, 1214, 755

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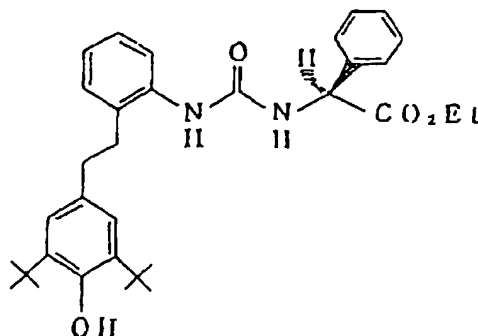
Example 69

(S)-N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(α -ethoxycarbonyl)benzylurea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using (S)- α -phenylglycine ethyl ester instead of decylamine.

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$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.44(d, J=8Hz, 1H), 7.19-7.33(m, 8H), 6.78(s, 2H), 5.90(s, 1H), 5.74(d, J=7Hz, 1H), 5.59(d, J=8Hz, 1H), 5.16(s, 1H), 4.10-4.24(m, 2H), 2.89-2.92(m, 2H), 2.82-2.85(m, 2H), 1.43(s, 18H), 1.21(t, J=7Hz, 3H)

$\text{IR}(\text{cm}^{-1})$ 3636, 3294, 1737, 1643, 1542, 1435, 1233, 1181, 754

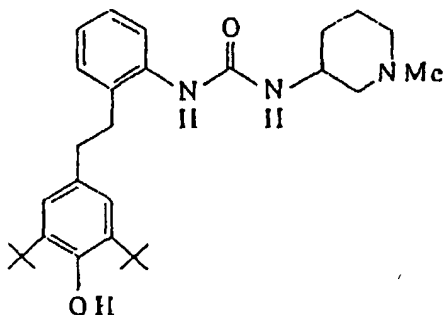
Example 70

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(1-methyl-3-piperidyl)urea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 3-amino-1-methylpiperidine instead of decylamine.

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$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.45(d, $J=8\text{Hz}$, 1H), 7.16-7.26(m, 3H), 6.92(s, 2H), 6.35(bs, 1H), 5.40(bs, 1H), 5.17(s, 1H), 3.45(bs, 1H), 3.18-3.23(m, 1H), 2.93-3.01(m, 1H), 2.83-2.92(m, 4H), 2.45-2.51(m, 1H), 2.34(s, 3H), 2.18-2.27(m, 1H), 1.82-1.95(m, 1H), 1.60-1.73(m, 3H), 1.46(s, 18H)
 $\text{IR}(\text{cm}^{-1})$ 3638, 3250, 1643, 1548, 1436, 1235, 910, 733

Example 71

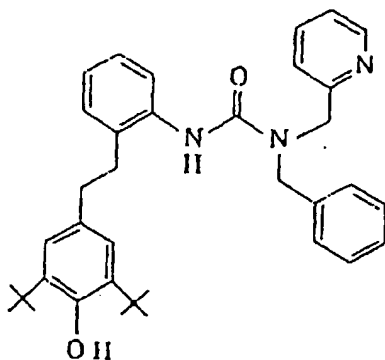
30

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-benzyl-N'-(2-pyridylmethyl)urea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using N-benzyl-2-pyridylmethylamine instead of decylamine.

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$^1\text{H-NMR}$ (δ ppm, CDCl_3) 9.20(bs, 1H), 7.92(d, $J=4\text{Hz}$, 1H), 7.78(d, $J=7\text{Hz}$, 1H), 7.52(ddd, $J=8, 8, 2\text{Hz}$, 1H), 7.19-7.30(m, 7H), 7.01-7.05(m, 2H), 6.93(s, 2H), 6.92-6.94(m, 1H), 5.06(s, 1H), 4.60(s, 2H), 4.41(s, 2H), 2.88-3.00(m, 4H), 1.36(s, 18H)
 $\text{IR}(\text{cm}^{-1})$ 3620, 3250, 2244, 1657, 1590, 1532, 1453, 1436, 1213, 752, 732

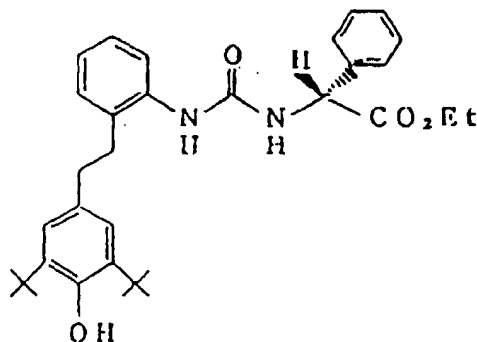
Example 72

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(α -ethoxycarbonyl)benzylurea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using (R)- α -phenylglycine ethyl ester instead of decylamine.

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$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.18-7.35(m, 9H), 6.77(s, 2H), 5.50(d, J=8Hz, 1H), 5.37(d, J=8Hz, 1H), 5.33(s, 1H), 5.09(s, 1H), 4.07-4.18(m, 2H), 2.78-2.84(m, 4H), 1.35(s, 18H), 1.17(t, J=7Hz, 3H)
 $\text{IR}(\text{cm}^{-1})$ 3636, 3330, 1739, 1640, 1542, 1436, 1234, 1180, 935, 751, 698

Example 73

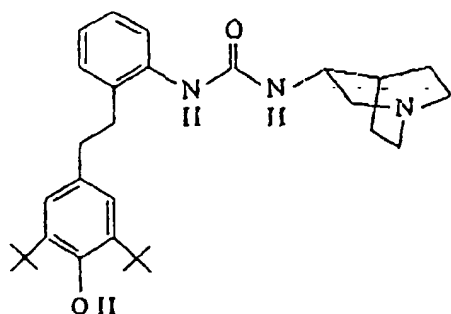
30

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(1-azabicyclo[2.2.2]octyl)urea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 3-amino-1-azabicyclo[2.2.2]octane instead of decylamine.
 m.p. 227-229°C

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$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.21-7.27(m, 4H), 6.77(s, 2H), 5.11(s, 1H), 5.07(s, 1H), 4.43(d, J=7Hz, 1H), 3.78-3.85(m, 1H), 3.28(ddd, J=14, 10, 2Hz, 1H), 2.65-2.89(m, 8H), 2.29-2.33(m, 1H), 1.85-1.87(m, 1H), 1.55-1.70(m, 4H), 1.38(s, 18H)
 $\text{IR}(\text{cm}^{-1})$ 3636, 3368, 3260, 1640, 1587, 1564, 1434, 1237, 1122, 765, 753

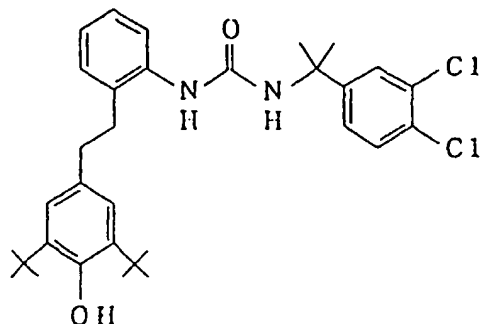
Example 74

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-[2-(3,4-dichlorophenyl)-2-propyl]urea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 3,4-dichloro- α,α -dimethylbenzylamine instead of decylamine.
m.p. 203-205°C

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$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.41(d, $J=2\text{Hz}$, 1H), 7.16-7.32(m, 6H), 6.81(s, 2H), 5.17(s, 1H), 5.11(s, 1H), 4.60(s, 1H), 2.79-2.83(m, 4H), 1.56(s, 6H), 1.39(s, 18H)
IR(cm^{-1}) 3638, 3352, 3282, 1644, 1564, 1558, 1437, 1235, 1171, 1030, 768, 745

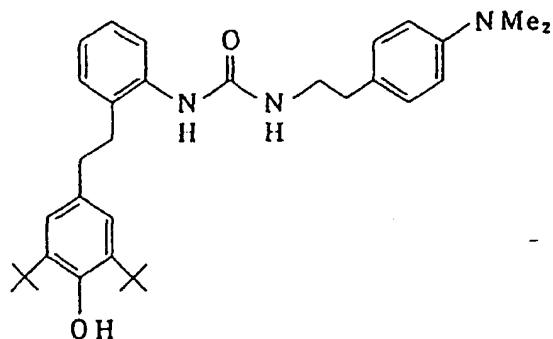
30 Example 75

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(4-dimethylaminophenethyl)urea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 4-dimethylaminophenethylamine instead of decylamine.

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$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.11-7.24(m, 4H), 6.96(d, $J=9\text{Hz}$, 2H), 6.77(s, 2H), 6.62(s, 2H), 5.09(s, 1H), 5.08(s, 1H), 4.03(t, $J=6\text{Hz}$, 1H), 3.33(td, $J=7, 6\text{Hz}$, 2H), 2.89(s, 6H), 2.72-2.86(m, 4H), 2.64(t, $J=7\text{Hz}$, 2H), 1.37(s, 18H)
IR(cm^{-1}) 3640, 3342, 2940, 1640, 1562, 1521, 1439, 1232, 660, 643

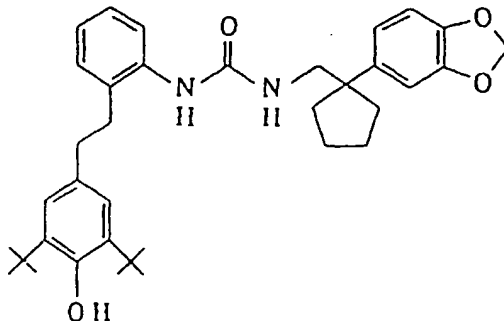
Example 76

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-[[1-(3,4-methylenedioxyphenyl)cyclopentyl]methyl]urea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 5-[1-(aminomethyl)cyclopentyl]-1,3-dioxindane instead of decylamine. m.p. 188-189°C

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$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.12-7.22(m, 3H), 7.03(d, $J=7\text{Hz}$, 1H), 6.75(s, 2H), 6.59(d, $J=2\text{Hz}$, 1H), 6.57(d, $J=8\text{Hz}$, 1H), 6.47(dd, $J=8, 2\text{Hz}$, 1H), 5.88(s, 2H), 5.08(s, 1H), 5.00(s, 1H), 3.95-4.00(m, 1H), 3.21(d, $J=5\text{Hz}$, 2H), 2.70-2.80(m, 4H), 1.55-1.85(m, 8H), 1.36(s, 18H)

$\text{IR}(\text{cm}^{-1})$ 3640, 3388, 3328, 1645, 1561, 1488, 1435, 1363, 1234, 1042, 940, 760

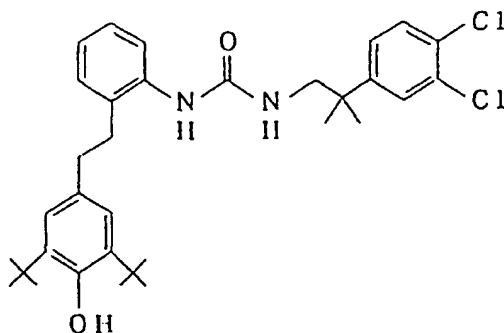
30 Example 77

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-[2-(3,4-dichlorophenyl)-2-methylpropyl]urea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 3,4-dichloro- β , β -dimethylphenethylamine instead of decylamine.
m.p. 165-167°C

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$^1\text{H-NMR}$ (δ ppm, CDCl_3) 6.95-7.29(m, 7H), 6.73(s, 2H), 5.09(s, 1H), 4.90-5.00(m, 1H), 3.96(bs, 1H), 3.29(d, $J=6\text{Hz}$, 2H), 2.65-2.75(m, 4H), 1.35(s, 18H), 1.23(s, 6H)

$\text{IR}(\text{cm}^{-1})$ 3638, 3364, 1646, 1587, 1563, 1475, 1437, 1235, 762

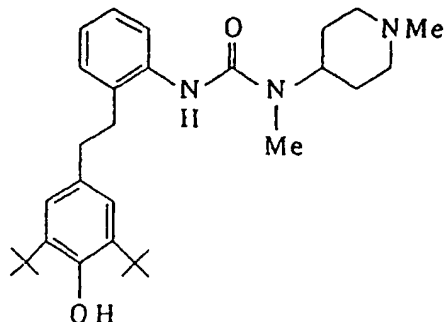
Example 78

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-methyl-N'-(1-methyl-4-piperidyl)urea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 1-methyl-4-(methyl-amino)piperidine instead of decylamine.

25 $^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.63(d, $J=7\text{Hz}$, 1H), 7.19-7.26(m, 2H), 7.10(ddd, $J=7, 7, 1\text{Hz}$, 1H), 6.79(s, 2H), 5.63(s, 1H), 5.08(s, 1H), 4.20-4.27(m, 1H), 2.85-2.90(m, 2H), 2.82(s, 4H), 2.48(s, 3H), 2.28(s, 3H), 1.98-2.07(m, 2H), 1.55-1.90(m, 4H), 1.35(s, 18H)
 IR(cm^{-1}) 3424, 1638, 1511, 1484, 1450, 1436, 1287, 1042, 754

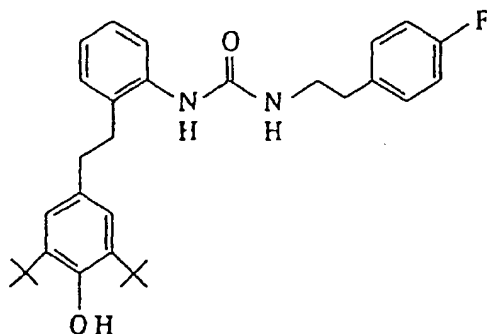
30 Example 79

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(4-fluorophenethyl)urea

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50 The title compound was prepared in a similar manner to that mentioned in Example 11, using 4-fluorophenethyl-amine instead of decylamine. m.p. 177-179°C

55 $^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.03-7.26(m, 6H), 6.89-6.93(m, 2H), 6.76(m, 2H), 5.10(s, 1H), 4.94(s, 1H), 4.15-4.20(m, 1H), 3.35(q, $J=7\text{Hz}$, 2H), 2.76-2.82(m, 4H), 2.71(t, $J=7\text{Hz}$, 2H), 1.36(s, 18H)
 IR(cm^{-1}) 3636, 3348, 1643, 1563, 1511, 1438, 1234, 831, 747

Example 80

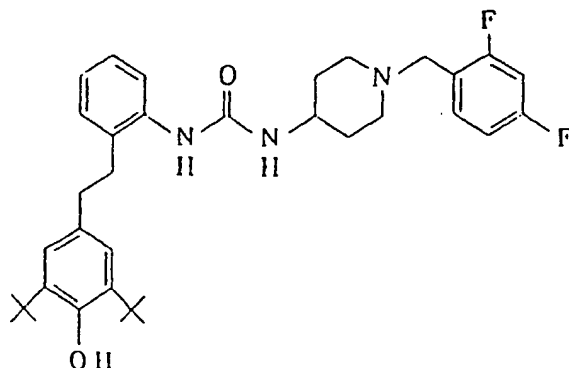
N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-[1-(2,4-difluorobenzyl)-4-piperidyl]urea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 4-amino-1-(2,4-difluorobenzyl)piperidine instead of decylamine.

m.p. 157-158°C

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$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.15-7.36(m, 5H), 6.89-6.72(m, 4H), 5.11(s, 1H), 4.97(s, 1H), 4.09(d, $J=8\text{Hz}$, 1H), 3.57-3.72(m, 1H), 3.47(s, 2H), 2.68-2.88(m, 6H), 2.14-2.20(m, 2H), 1.82-1.95(m, 2H), 1.58-1.74(m, 2H), 1.20-1.40(m, 2H), 1.37(s, 18H)

$\text{IR}(\text{cm}^{-1})$ 3640, 3370, 3250, 2960, 1690, 1650, 1590, 1565, 1505, 1235, 850, 760

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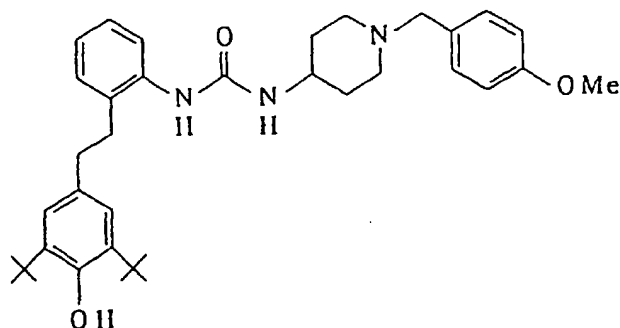
Example 81

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-[1-(4-methoxybenzyl)-4-piperidyl]urea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 4-amino-1-(4-methoxybenzyl)piperidine instead of decylamine.

m.p. 152-153°C

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$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.14-7.30(m, 6H), 6.74-6.88(m, 4H), 5.11(s, 1H), 4.97(s, 1H), 4.09(d, $J=8\text{Hz}$, 1H), 3.79(s, 3H), 3.56-3.72(m, 1H), 3.38(s, 2H), 2.67-2.88(m, 6H), 1.96-2.09(m, 2H), 1.82-1.92(m, 2H), 1.37(s, 18H), 1.18-1.35(m, 2H)

$\text{IR}(\text{cm}^{-1})$ 3640, 3360, 3260, 2950, 1645, 1595, 1565, 1515, 1245, 1045, 760

Example 82

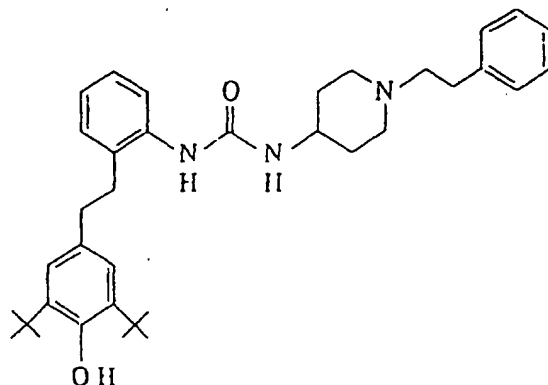
N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(1-phenethyl-4-piperidyl)urea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 4-amino-1-phenethyl-piperidine instead of decylamine. m.p. 175-176°C

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$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.15-7.31(m, 9H), 6.78(s, 2H), 5.12(s, 1H), 5.01(s, 1H), 4.13(d, $J=8\text{Hz}$, 1H), 3.58-3.73(m, 1H), 2.72-2.91(m, 8H), 2.50-2.57(m, 2H), 2.05-2.16(m, 2H), 1.38(s, 18H), 1.24-1.35(m, 2H)
 $\text{IR}(\text{cm}^{-1})$ 3640, 3340, 2950, 1640, 1590, 1565, 1435, 1235, 770, 750, 700

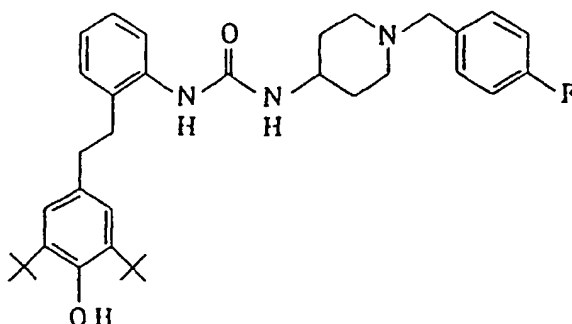
30 Example 83

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(1-(4-fluorobenzyl)-4-piperidyl)urea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 4-amino-1-(4-fluorobenzyl)piperidine instead of decylamine.

m.p. 174-175°C

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$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.16-7.29(m, 6H), 6.93-7.00(m, 2H), 6.77(s, 2H), 5.11(s, 1H), 4.97(s, 1H), 4.09(d, $J=8\text{Hz}$, 1H), 3.57-3.71(m, 1H), 3.39(s, 2H), 2.66-2.87(m, 6H), 1.98-2.08(m, 2H), 1.82-1.90(m, 2H), 1.37(s, 18H), 1.22-1.34(m, 2H)
 $\text{IR}(\text{cm}^{-1})$ 3645, 3370, 2950, 1540, 1590, 1560, 1510, 1225, 750

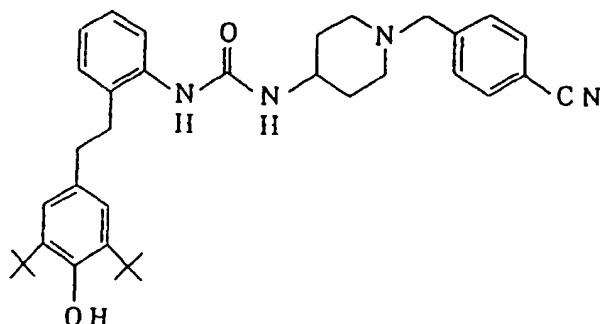
Example 84

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-[1-(4-cyanobenzyl)-4-piperidyl]urea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 4-amino-1-(4-cyanobenzyl)piperidine instead of decylamine. m.p. 197-198°C

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$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.58(d, $J=8\text{Hz}$, 2H), 7.40(d, $J=8\text{Hz}$, 2H), 7.17-7.29(m, 4H), 6.77(s, 2H), 5.12(s, 1H), 4.97(s, 1H), 4.10(d, $J=8\text{Hz}$, 1H), 3.59-3.72(m, 1H), 3.48(s, 2H), 2.75-2.87(m, 4H), 2.64-2.73(m, 2H), 2.03-2.13(m, 2H), 1.83-1.91(m, 2H), 1.37(s, 18H), 1.23-1.35(m, 2H)
 $\text{IR}(\text{cm}^{-1})$ 3580, 3355, 3250, 2960, 2240, 1645, 1590, 1560, 1235, 825, 765, 550

Example 85

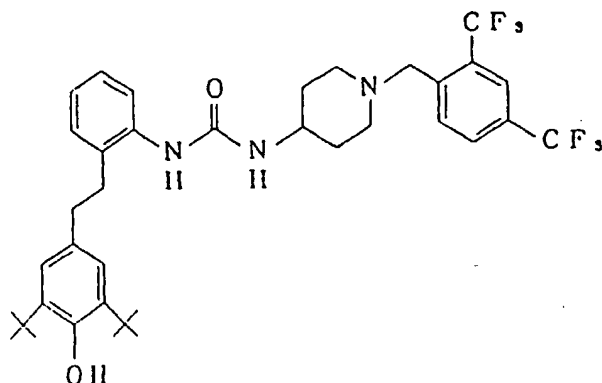
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N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-[1-[2,4-bis(trifluoromethyl)benzyl]-4-piperidyl]urea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 4-amino-1-[2,4-bis(trifluoromethyl)benzyl]piperidine instead of decylamine. m.p. 156-157°C

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$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.92(d, $J=8\text{Hz}$, 1H), 7.85(s, 1H), 7.73(d, $J=8\text{Hz}$, 1H), 7.17-7.29(m, 4H), 6.78(s, 2H), 5.12(s, 1H), 4.98(s, 1H), 4.11(d, $J=8\text{Hz}$, 1H), 3.61-3.74(m, 1H), 3.64(s, 2H), 2.75-2.88(m, 4H), 2.64-2.73(m, 2H), 2.13-2.23(m, 2H), 1.84-1.92(m, 2H), 1.38(s, 18H), 1.27-1.36(m, 2H)
 $\text{IR}(\text{cm}^{-1})$ 3645, 3350, 2955, 1600, 1565, 1440, 1350, 1280, 1175, 1130, 1060, 750, 680

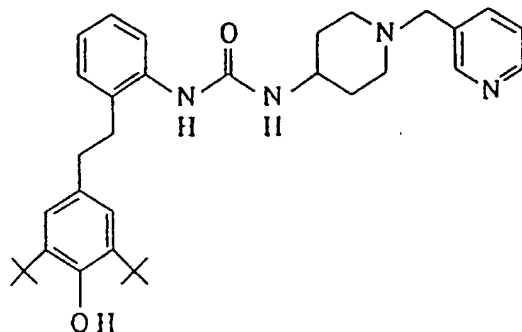
Example 86

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-[1-(3-pyridylmethyl)-4-piperidyl]urea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 4-amino-1-(3-pyridylmethyl)piperidine instead of decylamine.
m.p. 156-158°C

25

$^1\text{H-NMR}$ (δ ppm, CDCl_3) 8.46-8.52(m, 2H), 7.60(d, $J=8\text{Hz}$, 1H), 7.16-7.28(m, 5H), 6.77(s, 2H), 5.12(s, 1H), 5.02(s, 1H), 4.13(d, $J=8\text{Hz}$, 1H), 3.58-3.72(m, 1H), 3.45(s, 2H), 2.67-2.87(m, 6H), 2.03-2.12(m, 2H), 1.82-1.90(m, 2H), 1.37(s, 18H), 1.22-1.37(m, 2H)
 $\text{IR}(\text{cm}^{-1})$ 3632, 3362, 2950, 1645, 1561, 1433, 1232, 759, 713

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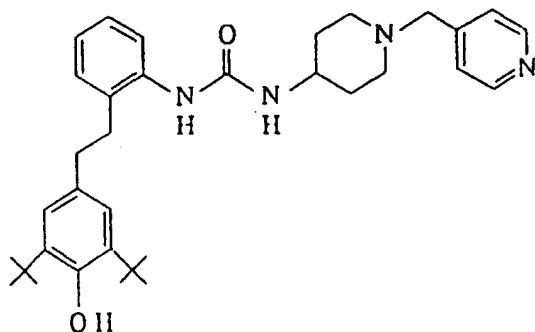
Example 87

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-[1-(4-pyridylmethyl)-4-piperidyl]urea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 4-amino-1-(4-pyridylmethyl)piperidine instead of decylamine.
m.p. 156-158°C

55

$^1\text{H-NMR}$ (δ ppm, CDCl_3) 8.51(dd, $J=4$, 2Hz, 2H), 7.16-7.28(m, 6H), 6.77(s, 2H), 5.12(s, 1H), 5.00(s, 1H), 4.12(d, $J=8\text{Hz}$, 1H), 3.60-3.72(m, 1H), 3.44(s, 2H), 2.74-2.88(m, 4H), 2.66-2.74(m, 2H), 2.04-2.14(m, 2H), 1.83-1.92(m, 2H), 1.38(s, 18H), 1.25-1.38(m, 2H)
 $\text{IR}(\text{cm}^{-1})$ 3630, 3292, 2948, 1620, 1560, 1435, 1237, 1109, 759

Example 88

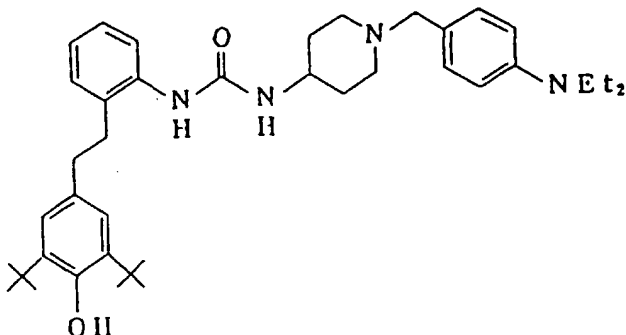
N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-[1-(4-diethylaminobenzyl)-4-piperidyl]urea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 4-amino-1-(4-diethylaminobenzyl)piperidine instead of decylamine.
m.p. 138-141°C

30

¹H-NMR(δ ppm, CDCl₃) 7.16-7.27(m, 4H), 7.09(d, J=8Hz, 2H), 6.77(s, 2H), 6.60(d, J=8Hz, 2H), 5.11(s, 1H), 4.99(s, 1H), 4.12(bd, J=7Hz, 1H), 3.58-3.70(m, 1H), 3.28-3.40(m, 6H), 2.73-2.86(m, 6H), 1.98-2.08(m, 2H), 1.82-1.89(m, 2H), 1.37(s, 18H), 1.25-1.37(m, 2H), 1.14(t, J=7Hz, 6H)
IR(cm⁻¹) 3630, 3410, 2950, 1641, 1553, 1520, 1232, 758

Example 89

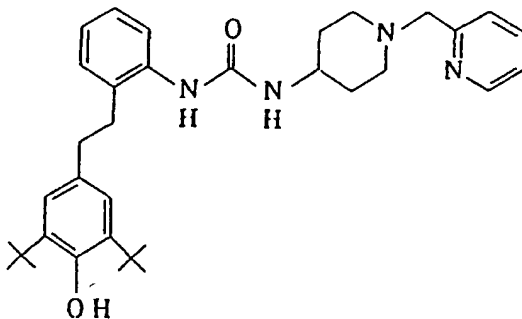
N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-[1-(2-pyridylmethyl)-4-piperidyl]urea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 4-amino-1-(2-pyridylmethyl)piperidine instead of decylamine.
m.p. 106-109°C

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¹H-NMR(δ ppm, CDCl₃) 8.54(d, J=4Hz, 1H), 7.58-7.65(m, 1H), 7.33(d, J=8Hz, 1H), 7.12-7.27(m, 6H), 6.77(s, 2H), 5.11(s, 1H), 5.01(s, 1H), 4.14(d, J=7Hz, 1H), 3.61-3.73(m, 1H), 3.59(s, 2H), 2.70-2.86(m, 6H), 2.12-2.21(m, 2H), 1.83-1.91(m, 2H), 1.37(s, 18H), 1.30-1.42(m, 2H)
IR(cm⁻¹) 3630, 3330, 2948, 1639, 1589, 1543, 1436, 1233, 1121, 756

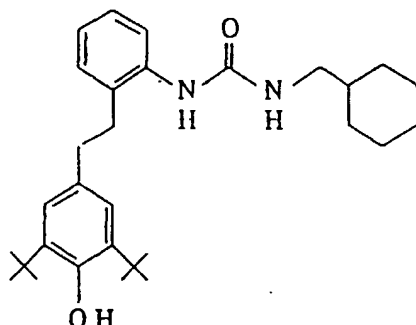
Example 90

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(cyclohexylmethyl)urea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using aminomethylcyclohexane instead of decylamine. m.p. 208-210°C

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$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.18-7.24(m, 4H), 6.78(s, 2H), 5.11(s, 1H), 4.98(bs, 1H), 4.18-4.28(m, 1H), 2.97(t, J=6Hz, 2H), 2.74-2.90(m, 4H), 1.55-1.70(m, 5H), 1.38(s, 18H), 1.08-1.30(m, 4H), 0.78-0.90(m, 2H)
 $\text{IR}(\text{cm}^{-1})$ 3616, 3304, 2922, 1627, 1579, 1435, 1233

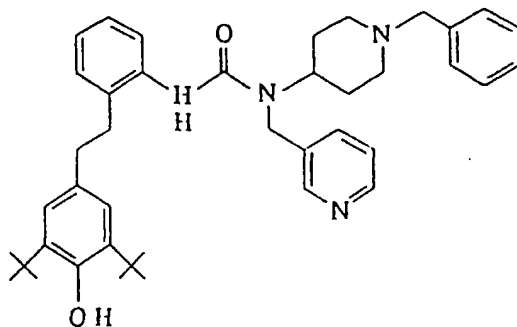
Example 91

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(1-benzyl-4-piperidyl)-N''-(3-pyridylmethyl)urea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 1-benzyl-4-(3-pyridylmethylamino)piperidine instead of decylamine.
 m.p. 127-130°C

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$^1\text{H-NMR}$ (δ ppm, CDCl_3) 8.55(d, J=2Hz, 1H), 8.41(dd, J=5, 2Hz, 1H), 7.65(d, J=8Hz, 1H), 7.59(d, J=8Hz, 1H), 7.13-7.30(m, 6H), 7.18(m, 1H), 7.10(dd, J=8, 5Hz, 1H), 7.01(d, J=4Hz, 2H), 6.75(s, 2H), 5.90(bs, 1H), 5.11(s, 1H), 4.45(s, 2H), 4.22-4.33(m, 1H), 3.47(s, 2H), 2.86-2.97(m, 2H), 2.61(t, J=7Hz, 2H), 2.44(t, J=7Hz, 2H), 2.00-2.14(m, 2H), 1.60-1.86(m, 4H), 1.38(s, 18H)
 $\text{IR}(\text{cm}^{-1})$ 3450, 3290, 1628, 1512, 1264, 1121, 1029, 742

Example 92

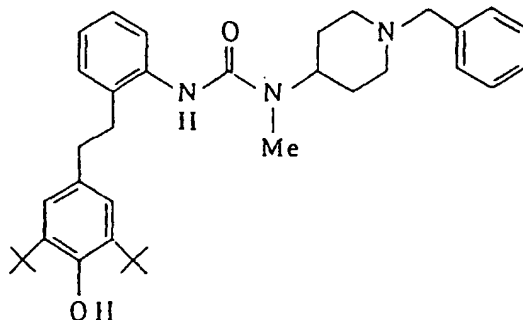
N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(1-benzyl-4-piperidyl)-N'-methylurea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 1-benzyl-4-(methylamino)piperidine instead of decylamine.
m.p. 144-146°C

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¹H-NMR(δ ppm, CDCl₃) 7.62(d, J=8Hz, 1H), 7.10-7.30(m, 7H), 7.10(d, J=7Hz, 1H), 6.78(s, 2H), 5.62(bs, 1H), 5.08(s, 1H), 4.23(s, 1H), 3.48(s, 2H), 2.86-2.98(m, 2H), 2.81(s, 4H), 2.50(s, 3H), 1.98-2.10(m, 2H), 1.50-1.70(m, 4H), 1.35(s, 18H)
IR(cm⁻¹) 3328, 2954, 1632, 1512, 1196, 1041, 755, 701

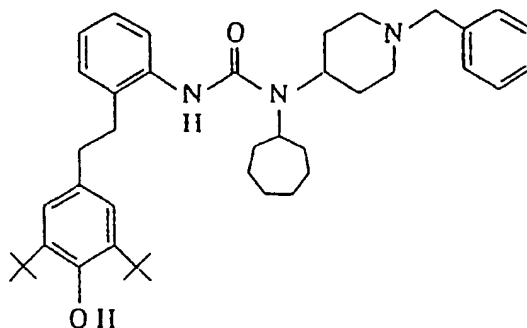
Example 93

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(1-benzyl-4-piperidyl)-N'-cycloheptylurea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 1-benzyl-4-(cycloheptylamino)piperidine instead of decylamine.
m.p. 107-109°C

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¹H-NMR(δ ppm, CDCl₃) 7.72(d, J=8Hz, 1H), 7.23-7.36(m, 5H), 7.19(t, J=7Hz, 1H), 7.13(d, J=6Hz, 1H), 7.02(t, J=7Hz, 1H), 6.93(s, 2H), 6.12(bs, 1H), 5.05(s, 1H), 4.04-4.154(m, 1H), 3.49(s, 2H), 3.37-3.50(m, 1H), 2.90-3.00(m, 2H), 2.84(s, 4H), 1.97-2.10(m, 4H), 1.78-1.89(m, 4H), 1.20-1.65(m, 28H)
IR(cm⁻¹) 3476, 2922, 1662, 1528, 1454, 1236, 753

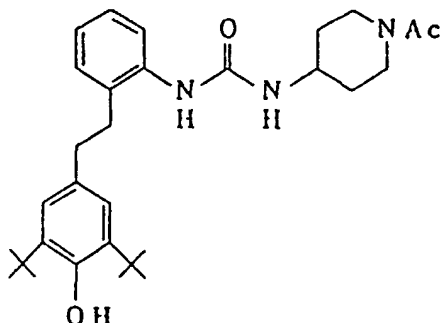
Example 94

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(1-acetyl-4-piperidyl)urea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 1-acetyl-4-aminopiperidine instead of decylamine. m.p. 218-221°C

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$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.15-7.29(m, 4H), 6.76(s, 2H), 5.13(s, 1H), 4.93(bs, 1H), 4.43-4.52(m, 1H), 4.05-4.13(m, 1H), 3.76-3.90(m, 1H), 3.66-3.73(m, 1H), 3.04-3.14(m, 1H), 2.71-2.85(m, 4H), 2.58-2.70(m, 1H), 2.05(s, 3H), 1.95-2.06(m, 1H), 1.82-1.90(m, 1H), 1.37(s, 18H), 1.10-1.20(m, 2H)
 $\text{IR}(\text{cm}^{-1})$ 3302, 2952, 1629, 1561, 1434, 1234

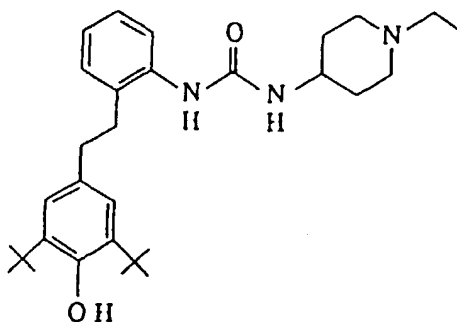
30 Example 95

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(1-ethyl-4-piperidyl)urea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 4-amino-1-ethylpiperidine instead of decylamine. m.p. 182-184°C

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$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.10-7.30(m, 4H), 6.77(s, 2H), 5.11(s, 1H), 5.00(bs, 1H), 4.14(bd, $J=8\text{Hz}$, 1H), 3.58-3.72(m, 1H), 2.70-2.90(m, 6H), 2.39(q, $J=7\text{Hz}$), 1.97-2.12(m, 2H), 1.85-1.97(m, 2H), 1.37(s, 18H), 1.30-1.40(m, 2H), 1.07(t, $J=7\text{Hz}$, 3H)
 $\text{IR}(\text{cm}^{-1})$ 3362, 2950, 1640, 1563, 1435, 1235

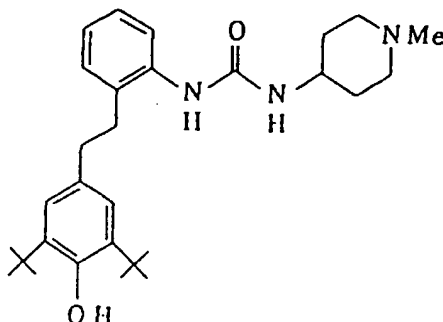
Example 96

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(1-methyl-4-piperidyl)urea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 4-amino-1-methyl-piperidine instead of decylamine. m.p. 193-195°C

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$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.15-7.25(m, 4H), 6.77(s, 2H), 5.12(s, 1H), 4.97(bs, 1H), 4.10(bd, $J=8\text{Hz}$, 1H), 3.58-3.70(m, 1H), 2.70-2.85(m, 6H), 2.25(s, 3H), 2.02-2.12(m, 2H), 1.84-1.93(m, 2H), 1.38(s, 18H), 1.30-1.43(m, 2H)
 $\text{IR}(\text{cm}^{-1})$ 3360, 2944, 1639, 1562

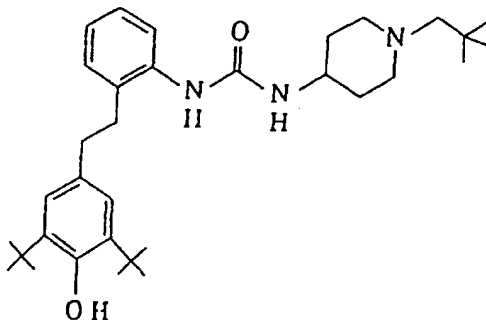
Example 97

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(1-(2,2-dimethylpropyl)-4-piperidyl)urea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 4-amino-1-(2,2-dimethylpropyl)piperidine instead of decylamine.

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$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.18-7.26(m, 4H), 6.78(s, 2H), 5.11(s, 1H), 5.06(bs, 1H), 4.12(bd, $J=8\text{Hz}$, 1H), 3.53-3.65(m, 1H), 2.75-2.90(m, 4H), 2.60-2.68(m, 2H), 2.22-2.32(m, 2H), 1.98(s, 2H), 1.73-1.83(m, 2H), 1.38(s, 18H), 1.20-1.40(m, 2H), 0.81(s, 9H)
 $\text{IR}(\text{cm}^{-1})$ 3322, 2952, 1638, 1536, 1435, 1234

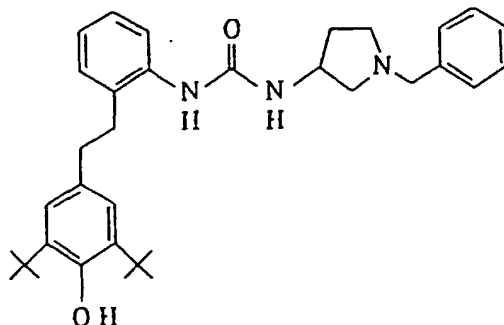
Example 98

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(1-benzyl-3-pyrrolidiny)urea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 3-amino-1-benzylpyrrolidine instead of decylamine.

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$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.10-7.30(m, 9H), 6.78(s, 2H), 5.37(bs, 1H), 5.10(s, 1H), 4.71(bd, $J=8\text{Hz}$, 1H), 4.23-4.34(m, 1H), 3.55(d, $J=13\text{Hz}$, 1H), 3.50(d, $J=13\text{Hz}$, 1H), 2.70-2.81(m, 6H), 2.49(d, $J=4\text{Hz}$, 2H), 2.14-2.36(m, 2H), 1.37(s, 18H)

$\text{IR}(\text{cm}^{-1})$ 3634, 3304, 2954, 1638, 1559, 1436, 1234, 749, 699

Example 99

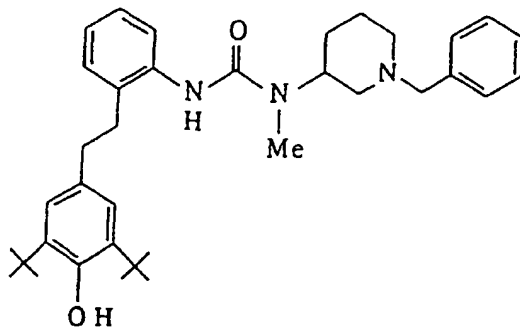
30

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(1-benzyl-3-piperidyl)-N'-methylurea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 3-amino-1-benzylpiperazine instead of decylamine.

$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.59(d, $J=8\text{Hz}$, 1H), 7.15-7.40(m, 7H), 7.08(t, $J=7\text{Hz}$, 1H), 6.79(s, 2H), 5.72(bs, 1H), 5.06(s, 1H), 4.22-4.34(m, 1H), 3.48(s, 2H), 2.70-2.80(m, 6H), 2.58(s, 3H), 1.60-1.90(m, 4H), 1.30-1.46(m, 2H), 1.35(s, 18H)

$\text{IR}(\text{cm}^{-1})$ 3630, 3422, 2940, 1639, 1520, 1485, 1452, 1312, 1249, 1122, 752, 699

Example 100

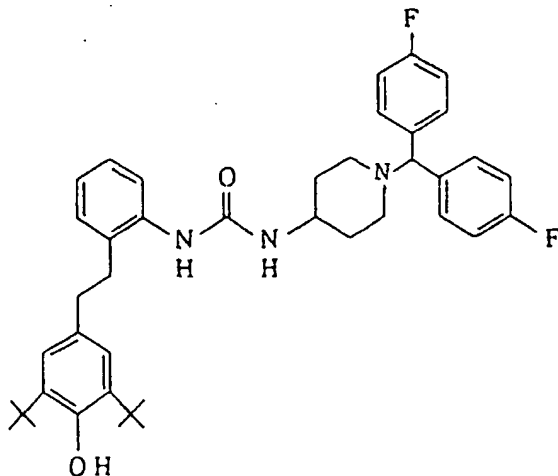
N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-[1-[bis(4-fluorophenyl)methyl]-4-piperidyl]urea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 4-amino-1-[bis(4-fluorophenyl)methyl]piperidine instead of decylamine.

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$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.65-7.80(m, 4H), 7.15-7.30(m, 4H), 7.12(t, J=7Hz, 2H), 6.84(d, J=9Hz, 2H), 6.77(s, 2H), 5.11(s, 1H), 5.01(bs, 1H), 4.13(t, J=7Hz, 2H), 3.75-3.95(m, 3H), 2.91-3.03(m, 2H), 2.75-2.90(m, 4H), 1.92-2.03(m, 2H), 1.25-1.40(m, 2H), 1.37(s, 18H)

IR(cm^{-1}) 3314, 2948, 1638, 1602, 1544, 1303, 1226, 1153, 768

Example 101

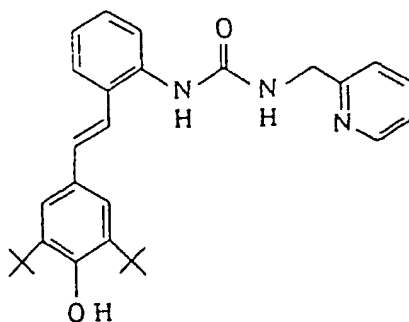
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N-[2-(3,5-di-tert-butyl-4-hydroxystyryl)phenyl]-N'-(2-pyridylmethyl)urea

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(1) To a solution of 4-(2-aminostyryl)-2,6-di-tert-butylphenol (4.85 g, 15.0 mmol) and diisopropylamine (1.72 g, 17.0 mmol) in methylene chloride (30 ml) was added dropwise under ice-cooling phenyl chloroformate (2.51 g, 16.0 mmol). The mixture was stirred for 7 hrs, while returning slowly to room temperature. To the mixture was added diisopropylamine (0.51 g, 5.0 mmol) and added dropwise under ice-cooling diisopropylamine (0.51 g, 5.0 mmol).

This mixture was stirred for 3 hrs, while returning slowly to room temperature. The reaction solution was washed with water and a saturated NaCl solution, dried over MgSO_4 and concentrated. Purification of the residue by a silica gel column chromatography gave N-[2-(3,5-di-tert-butyl-4-hydroxystyryl)phenyl]phenyl carbamate (6.65 g, 99%) as a viscous oil.

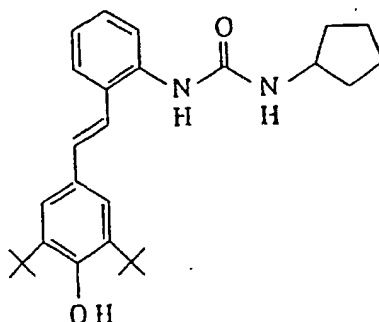
$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.91(b, 1H), 6.90-7.53(m, 13H), 5.35(s, 1H), 1.49(s, 18H)

(2) A solution of N-[2-(3,5-di-tert-butyl-4-hydroxystyryl)phenyl]phenyl carbamate (1.00 g, 2.25 mmol) and 2-(aminomethyl)pyridine (0.27 g, 2.50 mmol) in xylene (5 ml) was stirred at 80-100°C for 3 hrs. After distilling off the solvent, purification of the residue by a silica gel column chromatography afforded N-[2-(3,5-di-tert-butyl-4-hydroxystyryl)phenyl]-N'-(2-pyridylmethyl)urea (0.54 g, 71%) as crystals. m.p. 207-210°C

$^1\text{H-NMR}$ (δ ppm, CDCl_3) 8.37(d, J=4Hz, 1H), 7.59(dd, J=8, 2Hz, 1H), 7.51(d, J=7Hz, 1H), 7.43-7.50(m, 1H), 7.31(s, 2H), 7.16-7.28(m, 3H), 7.17(d, J=16Hz, 1H), 7.02-7.07(m, 1H), 6.99(d, J=16Hz, 1H), 6.68-6.91(m, 1H), 5.79-5.87(m, 1H), 5.32(s, 1H), 4.51(d, J=5Hz, 2H), 1.45(s, 18H)
 IR(cm^{-1}) 3350, 3270, 2960, 1640, 1560, 1475, 1440, 1235, 1010, 755, 740

Example 102

N-[2-(3,5-di-tert-butyl-4-hydroxystyryl)phenyl]-N'-cycloheptylurea



The title compound was prepared in a similar manner to that mentioned in Example 101, using cycloheptylamine instead of 2-(aminomethyl)pyridine.

m.p. 203-206°C

$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.61(d, J=8Hz, 1H), 7.38(d, J=8Hz, 1H), 7.33(s, 2H), 7.18-7.28(m, 2H), 7.06(d, J=16Hz, 1H), 7.00(d, J=16Hz, 1H), 6.05(s, 1H), 5.33(s, 1H), 4.48-4.55(m, 1H), 4.04-4.16(m, 1H), 1.88-2.00(m, 2H), 1.48-1.62(m, 4H), 1.47(s, 18H), 1.22-1.37(m, 2H)
 IR(cm^{-1}) 3630, 3310, 2950, 1630, 1560, 1440, 1235, 960, 745

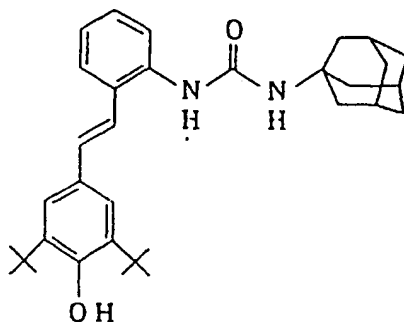
Example 103

N-[2-(3,5-di-tert-butyl-4-hydroxystyryl)phenyl]-N'-adamantylurea

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20 The title compound was prepared in a similar manner to that mentioned in Example 101, using 1-adamantanamine instead of 2-(aminomethyl)pyridine.
m.p. 205-211°C

25 ¹H-NMR(δ ppm, CDCl₃) 7.66(dd, J=7, 2Hz, 1H), 7.34(s, 2H), 7.29-7.36(m, 1H), 7.15-7.29(m, 2H), 7.06(d, J=16Hz, 1H), 7.00(d, J=16Hz, 1H), 5.90(s, 1H), 5.33(s, 1H), 4.34(s, 1H), 1.82-2.06(m, 9H), 1.52-1.67(m, 6H), 1.47(s, 18H)
IR(cm⁻¹) 3630, 3330, 2900, 1640, 1560, 1525, 1235, 740,

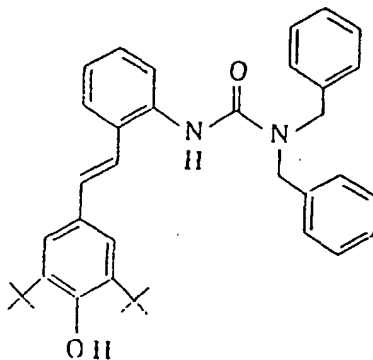
Example 104

30 N-[2-(3,5-di-tert-butyl-4-hydroxystyryl)phenyl]-N',N'-dibenzylurea

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50 The title compound was prepared in a similar manner to that mentioned in Example 101, using N,N-dibenzylamine instead of 2-(aminomethyl)pyridine.
m.p. 175-178°C

55 ¹H-NMR(δ ppm, CDCl₃) 7.79(dd, J=8, 1Hz, 1H), 7.36(dd, J=8, 1Hz, 1H), 7.02-7.30(m, 13H), 7.02-7.08(m, 1H), 6.78(d, J=16Hz, 1H), 6.65(d, J=16Hz, 1H), 5.31(s, 1H), 4.60(s, 4H), 1.47(s, 18H)
IR(cm⁻¹) 3420, 3390, 2940, 1660, 1580, 1520, 1450, 1435, 1230, 960, 755

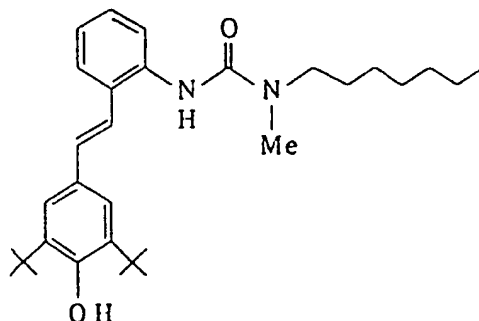
Example 105

N-[2-(3,5-di-tert-butyl-4-hydroxystyryl)phenyl]-N'-methyl-N'-heptylurea

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The title compound was prepared in a similar manner to that mentioned in Example 101, using N-methylheptylamine instead of 2-(aminomethyl)pyridine.

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$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.81(d, $J=8\text{Hz}$, 1H), 7.44(d, $J=8\text{Hz}$, 1H), 7.32(s, 2H), 7.22-7.27(m, 1H), 7.05-7.10(m, 1H), 7.00(d, $J=16\text{Hz}$, 1H), 6.93(d, $J=16\text{Hz}$, 1H), 6.36(s, 1H), 5.32(s, 1H), 3.34(d, $J=8\text{Hz}$, 2H), 3.02(s, 3H), 1.54-1.65(m, 2H), 1.47(s, 18H), 1.16-1.32(m, 8H), 0.84(t, $J=7\text{Hz}$, 3H)
 $\text{IR}(\text{cm}^{-1})$ 3640, 3450, 3300, 2960, 2930, 1640, 1580, 1520, 1485, 1440, 1240, 1155, 960, 750

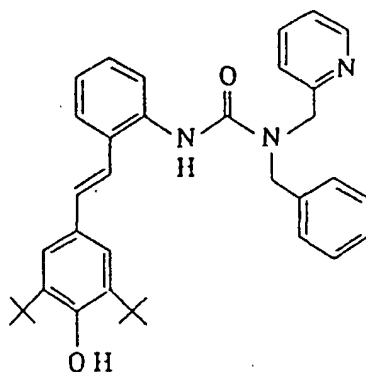
30 Example 106

N-[2-(3,5-di-tert-butyl-4-hydroxystyryl)phenyl]-N'-benzyl-N'-(2-pyridylmethyl)urea

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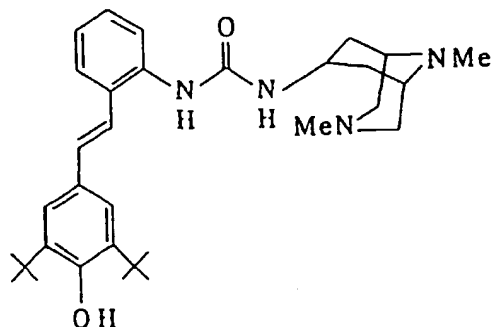
The title compound was prepared in a similar manner to that mentioned in Example 101, using 2-(benzylaminomethyl)pyridine instead of 2-(aminomethyl)pyridine.

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$^1\text{H-NMR}$ (δ ppm, CDCl_3) 9.74(b, 1H), 8.14(d, $J=4\text{Hz}$, 1H), 7.87(d, $J=8\text{Hz}$, 1H), 7.47-7.57(m, 1H), 7.18-7.34(m, 9H), 6.88-7.11(m, 4H), 5.26(s, 1H), 4.65(s, 2H), 4.49(s, 2H), 1.40(s, 18H)
 $\text{IR}(\text{cm}^{-1})$ 3390, 2950, 1660, 1580, 1525, 1455, 1230, 960, 755, 735, 700

Example 107

N-[2-(3,5-di-tert-butyl-4-hydroxystyryl)phenyl]-N'-(3,9-dimethyl-3,9-diazabicyclo[3.3.1]-7-nonyl)urea

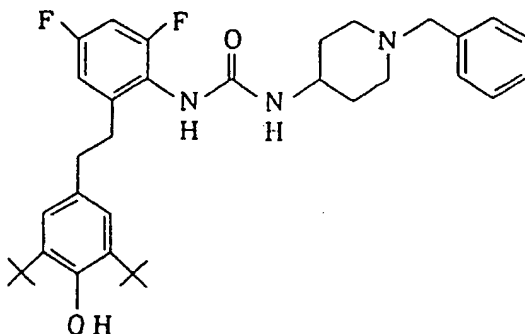


The title compound was prepared in a similar manner to that mentioned in Example 101, using 7-amino-3,9-dimethyl-3,9-diazabicyclo[3.3.1]nonane instead of 2-(aminomethyl)pyridine.
m.p. 188-191°C

$^1\text{H-NMR}$ (δ ppm, CDCl_3) 8.78(d, $J=10\text{Hz}$, 1H), 7.64(dd, $J=7$, 2Hz, 1H), 7.30-7.35(m, 3H), 7.13-7.27(m, 2H), 7.13(d, $J=2\text{Hz}$, 1H), 7.02(d, $J=2\text{Hz}$, 1H), 5.93(s, 1H), 5.35(s, 1H), 4.22-4.33(m, 1H), 2.66-2.72(m, 2H), 2.41(s, 3H), 2.22-2.40(m, 6H), 1.48(s, 3H), 1.47(s, 18H), 1.28-1.38(m, 2H)
IR(cm^{-1}) 3410, 2940, 1630, 1600, 1510, 1440, 1390, 1265, 1185, 965, 760

Example 108

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)-4,6-difluorophenyl]-N'-(1-benzyl-4-piperidyl)urea



(1) To a solution of 4-(2-amino-3,5-difluorophenethyl)-2,6-di-tert-butylphenol (1.37 g, 3.8 mmol) and diisopropylamine (0.50 g, 4.9 mmol) in methylene chloride (20 ml) was added dropwise under ice-cooling phenyl chloroformate (0.66 g, 4.2 mmol) and the mixture was stirred for 3 hrs, while returning slowly to room temperature. Diisopropylamine (0.19 g, 1.9 mmol) was further added and phenyl chloroformate (0.30 g, 1.9 mmol) was added dropwise under ice-cooling. The mixture was stirred for 3 hrs while returning slowly to room temperature. The reaction solution was washed with water and a saturated NaCl solution, dried over MgSO_4 and concentrated. Purification of the residue by silica gel column chromatography gave N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)-4,6-difluorophenyl]phenyl carbamate (1.82 g, 99%) as oil.

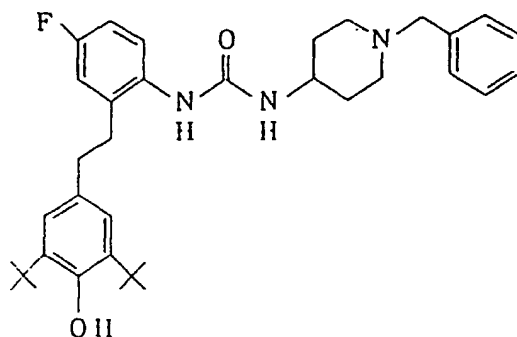
$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.04-7.42(m, 5H), 6.67-6.85(m, 4H), 5.16(s, 1H), 4.94(s, 1H), 2.76-3.02(m, 4H), 1.37(s, 18H)

(2) A solution of N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)-4,6-difluorophenyl]phenyl carbamate (1.82 g, 3.8 mmol) and 4-amino-1-benzylpyridine (0.72 g, 3.8 mmol) in toluene (10 ml) was stirred at 100-120°C for 2 hrs. After distilling off the solvent, purification of the residue by a silica gel column chromatography afforded N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)-4,6-difluorophenyl]-N'-(1-benzyl-4-piperidyl)urea (1.39 g, 64%) as a noncrystalline solid.

$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.20-7.30(m, 5H), 6.65-6.80(m, 4H), 5.12(s, 1H), 4.79(bs, 1H), 4.14(bd, $J=8\text{Hz}$, 1H), 3.54-3.66(m, 1H), 3.44(s, 2H), 2.84(d, $J=7\text{Hz}$, 2H), 2.70-2.79(m, 4H), 1.98-2.10(m, 2H), 1.80-1.92(m, 2H), 1.30-1.40(m, 20H)
 $\text{IR}(\text{cm}^{-1})$ 3638, 3316, 2952, 1639, 1562, 1494, 1436, 1235, 1122

Example 109

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)-4-fluorophenyl]-N'-(1-benzyl-4-piperidyl)urea



The title compound was prepared in a similar manner to that mentioned in Example 108, using 4-(2-amino-5-fluorophenethyl)-2,6-di-tert-butylphenol instead of 4-(2-amino-3,5-difluorophenethyl)-2,6-di-tert-butylphenol.
 m.p. 108-109°C

$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.21-7.31(m, 5H), 7.16(dd, $J=9$, 5Hz, 1H), 6.87-6.96(m, 2H), 6.77(s, 2H), 5.12(s, 1H), 4.86(s, 1H), 3.99(d, $J=8\text{Hz}$, 1H), 3.55-3.70(m, 1H), 3.44(s, 1H), 2.70-2.85(m, 6H), 2.05(t, $J=11\text{Hz}$, 2H), 1.85(d, $J=10\text{Hz}$, 2H), 1.38(s, 18H), 1.25-1.35(m, 2H)
 $\text{IR}(\text{cm}^{-1})$ 3636, 3280, 1634, 1561, 1495, 1435, 1234, 1213, 1120, 739, 699

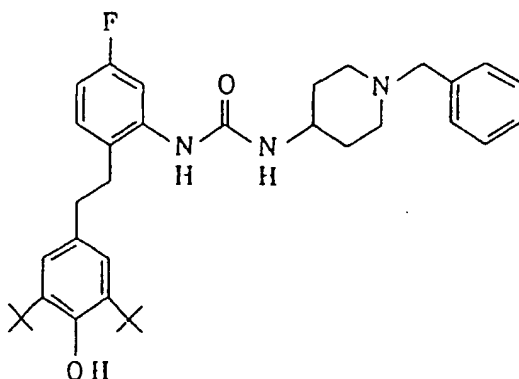
Example 110

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)-5-fluorophenyl]-N'-(1-benzyl-4-piperidyl)urea

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The title compound was prepared in a similar manner to that mentioned in Example 108, using 4-(2-amino-4-fluorophenethyl)-2,6-di-tert-butylphenol instead of 4-(2-amino-3,5-difluorophenethyl)-2,6-di-tert-butylphenol.

m.p. 118-119°C

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$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.20-7.32(m, 5H), 7.13-7.20(m, 2H), 6.84(dt, $J=3, 8\text{Hz}$, 1H), 6.78(s, 2H), 5.13(s, 1H), 5.01(s, 1H), 4.02(d, $J=8\text{Hz}$, 1H), 3.46-3.63(m, 1H), 3.46(s, 2H), 2.77(bs, 6H), 2.06(t, $J=11\text{Hz}$, 2H), 1.86(d, $J=11\text{Hz}$, 2H), 1.38(s, 18H), 1.30-1.40(m, 2H)

$\text{IR}(\text{cm}^{-1})$ 3630, 3350, 1640, 1602, 1563, 1434, 1233, 738, 700

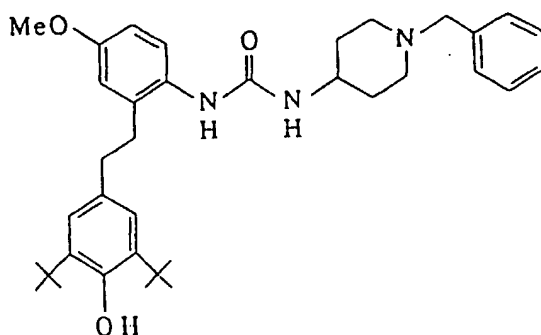
30 Example 111

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)-4-methoxyphenyl]-N'-(1-benzyl-4-piperidyl)urea

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The title compound was prepared in a similar manner to that mentioned in Example 108, using 4-(2-amino-5-methoxyphenethyl)-2,6-di-tert-butylphenol instead of 4-(2-amino-3,5-difluorophenethyl)-2,6-di-tert-butylphenol.

m.p. 174-175°C

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$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.20-7.30(m, 5H), 7.00-7.07(m, 1H), 6.78(s, 2H), 6.70-6.75(m, 2H), 5.09(s, 1H), 4.91(s, 1H), 4.05(d, $J=8\text{Hz}$, 1H), 3.79(s, 3H), 3.60-3.65(m, 1H), 3.43(s, 2H), 2.70-2.80(m, 6H), 2.05(t, $J=11\text{Hz}$, 2H), 1.85(d, $J=11\text{Hz}$, 2H), 1.38(s, 18H), 1.20-1.40(m, 2H)

$\text{IR}(\text{cm}^{-1})$ 3630, 3312, 1634, 1561, 1501, 1436, 1282, 1231, 1055, 880, 750, 710

Example 112

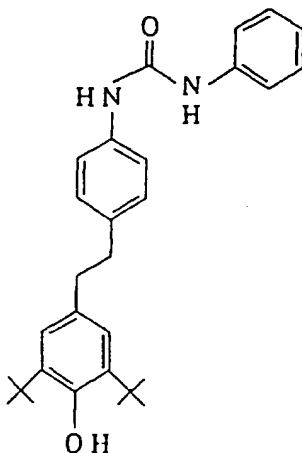
N-[4-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-phenylurea

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The title compound was prepared in a similar manner to that mentioned in Example 1, using 4-(4-aminophenethyl)-2,6-di-tert-butylphenol instead of 4-(2-aminophenethyl)-2,6-di-tert-butylphenol and using benzoic acid instead of 4-hexyloxybenzoic acid. m.p. 206-207°C

30

$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.22-7.38(m, 6H), 7.18(d, $J=9\text{Hz}$, 2H), 7.08-7.14(m, 1H), 6.55(bs, 1H), 6.47(bs, 1H), 2.77-2.92(m, 4H), 1.43(s, 18H)
 $\text{IR}(\text{cm}^{-1})$ 3640, 3330, 2960, 1655, 1605, 1565, 1440, 1320, 1240, 760, 695

Example 113

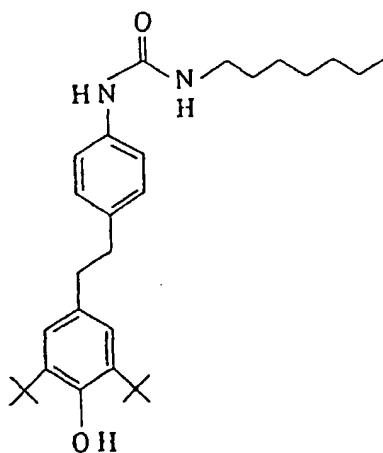
N-[4-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-heptylurea

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The title compound was prepared in a similar manner to that mentioned in Example 1, using 4-(4-aminophenethyl)-2,6-di-tert-butylphenol instead of 4-(2-aminophenethyl)-2,6-di-tert-butylphenol and n-octanoic acid instead of 4-hexyloxybenzoic acid. m.p. 151-152°C

EP 0 625 507 B1

$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.13-7.21(m, 4H), 6.95(s, 2H), 6.22(bs, 1H), 5.06(s, 1H), 4.73(bt, $J=5\text{Hz}$, 1H), 3.23(dt, $J=5, 7\text{Hz}$, 2H), 2.75-2.90(m, 42H), 1.45-1.54(m, 2H), 1.42(s, 18H), 1.21-1.36(m, 8H), 0.88(t, $J=7\text{Hz}$, 3H)
 $\text{IR}(\text{cm}^{-1})$ 3630, 3120, 2960, 2930, 2860, 1645, 1605, 1575, 1520, 1440, 1235

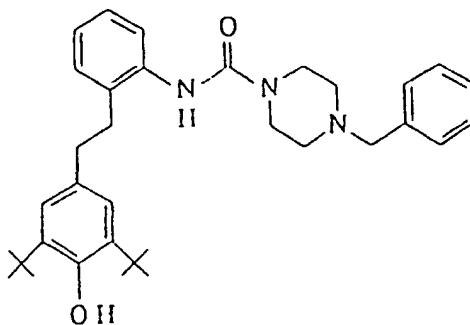
5 Example 114

1-Benzyl-4-[N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]carbamoyl]piperazine

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25 The title compound was prepared in a similar manner to that mentioned in Example 11, using 1-benzylpiperazine instead of decylamine. m.p. 70-72°C

$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.49-7.51(m, 1H), 7.09-7.33(m, 8H), 6.78(s, 2H), 5.61(s, 1H), 5.06(s, 1H), 3.50(s, 2H), 3.22(t, $J=5\text{Hz}$, 4H), 2.80(s, 4H), 2.39(t, $J=5\text{Hz}$, 4H), 1.33(s, 18H)
30 $\text{IR}(\text{cm}^{-1})$ 3636, 3310, 2952, 1635, 1516, 1435, 1234, 1001, 754

Example 115

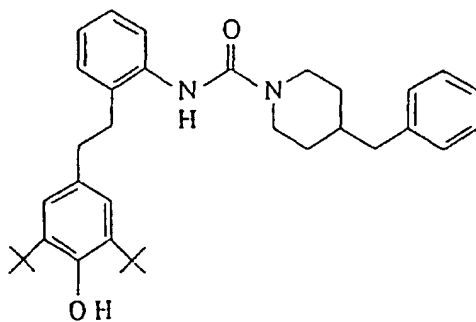
4-Benzyl-1-[N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]carbamoyl]piperidine

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 4-benzylpiperidine instead of decylamine.

$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.52(d, $J=8\text{Hz}$, 1H), 7.06-7.32(m, 8H), 6.79(s, 2H), 5.67(s, 1H), 5.06(s, 1H), 3.68-3.76(m, 2H), 2.81(s, 4H), 2.62-2.72(m, 2H), 2.53(t, $J=7\text{Hz}$, 4H), 1.50-1.73(m, 3H), 1.35(s, 18H), 1.10-1.23(m, 2H)
55 $\text{IR}(\text{cm}^{-1})$ 3645, 3440, 3330, 2960, 2925, 1645, 1525, 1455, 1440, 1250, 755, 705

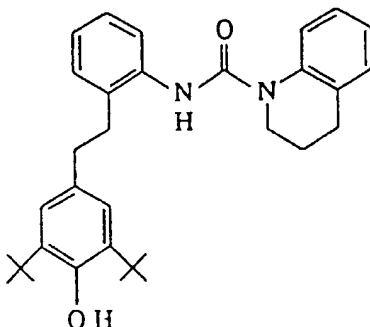
Example 116

1-[N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]carbamoyl]-1,2,3,4-tetrahydroquinoline

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 1,2,3,4-tetrahydroquinoline instead of decylamine.

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$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.82(d, $J=7\text{Hz}$, 1H), 7.36(d, $J=7\text{Hz}$, 1H), 7.13-7.21(m, 2H), 7.16(d, $J=7\text{Hz}$, 1H), 6.99-7.09(m, 3H), 6.89(bs, 1H), 6.82(s, 2H), 5.06(s, 1H), 3.80(t, $J=6\text{Hz}$, 2H), 2.78(t, $J=6\text{Hz}$, 2H), 2.69(s, 4H), 1.98(m, 2H), 1.39(s, 18H)

$\text{IR}(\text{cm}^{-1})$ 3630, 3434, 2946, 1671, 1524, 1492, 1435, 1304, 1236, 753

Example 117

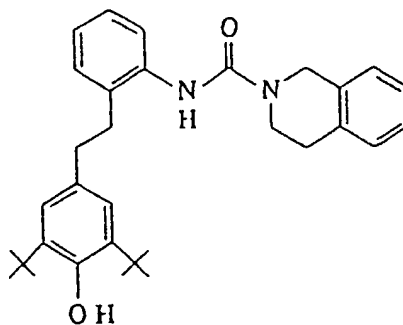
30

2-[N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]carbamoyl]-1,2,3,4-tetrahydroisoquinoline

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 1,2,3,4-tetrahydroisoquinoline instead of decylamine. m.p. 148-150°C

$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.55(d, $J=8\text{Hz}$, 1H), 7.10-7.26(m, 7H), 6.83(s, 1H), 5.73(bs, 1H), 5.10(s, 1H), 4.52(s, 2H), 3.44(t, $J=6\text{Hz}$, 2H), 2.86(t, $J=6\text{Hz}$, 2H), 2.84(s, 4H), 1.36(s, 18H)

$\text{IR}(\text{cm}^{-1})$ 3628, 3312, 1630, 1515, 1459, 1437, 1373, 1231, 747

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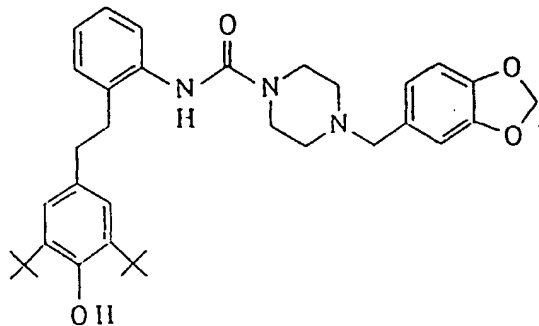
Example 118

1-[N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]carbamoyl]-4-(3,4-methylenedioxybenzyl)piperazine

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 1-(3,4-methylenedioxybenzyl)piperazine instead of decylamine.

m.p. 149-151°C

25

$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.50(d, $J=7\text{Hz}$, 1H), 7.18-7.23(m, 2H), 7.11(dd, $J=7, 7\text{Hz}$, 1H), 6.83(s, 1H), 6.70-6.76(m, 2H), 5.95(s, 2H), 5.61(bs, 1H), 5.06(s, 1H), 3.40(s, 2H), 3.22(t, $J=5\text{Hz}$, 4H), 2.80(s, 4H), 2.36(t, $J=5\text{Hz}$, 4H), 1.34(s, 18H)

$\text{IR}(\text{cm}^{-1})$ 3626, 3302, 2956, 1632, 1504, 1491, 1438, 1247, 1040, 999, 759

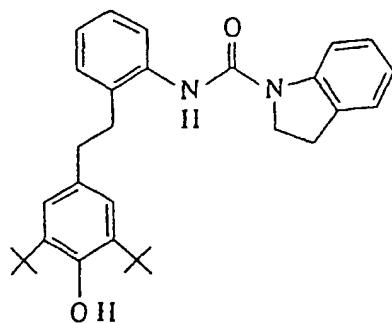
30 Example 119

1-[N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]carbamoyl]indoline

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The title compound was prepared in a similar manner to that mentioned in Example 11, using indoline instead of decylamine.

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$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.91(d, $J=8\text{Hz}$, 1H), 7.61(d, $J=8\text{Hz}$, 1H), 7.10-7.30(m, 2H), 6.91(dd, $J=8, 8\text{Hz}$, 2H), 6.81(d, $J=8\text{Hz}$, 2H), 6.78(s, 2H), 5.65(bs, 1H), 5.10(s, 1H), 3.57(t, $J=8\text{Hz}$, 2H), 3.14(t, $J=8\text{Hz}$, 2H), 2.86(s, 4H), 1.35(s, 18H)

$\text{IR}(\text{cm}^{-1})$ 3622, 3272, 2952, 1654, 1594, 1507, 1485, 1448, 1347, 1234, 753

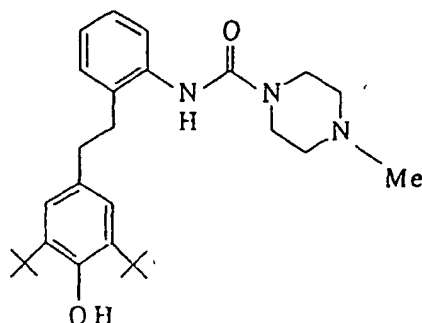
Example 120

1-[N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]carbamoyl]-4-methylpiperazine

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 1-methylpiperazine instead of decylamine. m.p. 134-137°C

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$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.47(d, $J=8\text{Hz}$, 1H), 7.17-7.26(m, 2H), 7.12(ddd, $J=7, 7, 2\text{Hz}$, 1H), 6.79(s, 2H), 5.56(s, 1H), 5.10(s, 1H), 3.25(t, $J=5\text{Hz}$, 4H), 2.82(s, 4H), 2.35(t, $J=5\text{Hz}$, 4H), 2.29(s, 3H), 1.37(s, 18H)
 $\text{IR}(\text{cm}^{-1})$ 3632, 3440, 2940, 1636, 1511, 1437, 1002, 750

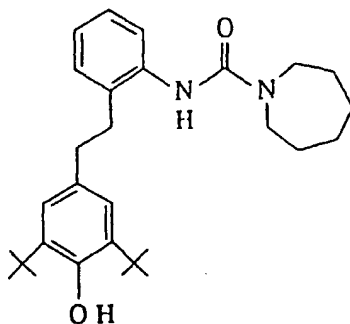
Example 121

1-[N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]carbamoyl]perhydroazepine

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The title compound was prepared in a similar manner to that mentioned in Example 11, using hexamethyleneimine instead of decylamine. m.p. 136-138°C

50

$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.67(dd, $J=7, 2\text{Hz}$, 1H), 7.17-7.24(m, 2H), 7.08(ddd, $J=7, 7, 2\text{Hz}$, 1H), 6.82(s, 2H), 5.78(s, 1H), 5.08(s, 1H), 3.26-3.34(m, 4H), 2.82(bs, 1H), 1.66-1.74(m, 4H), 1.52-1.59(m, 4H), 1.37(s, 18H)
 $\text{IR}(\text{cm}^{-1})$ 3460, 1660, 1587, 1525, 1453, 1436, 755

55

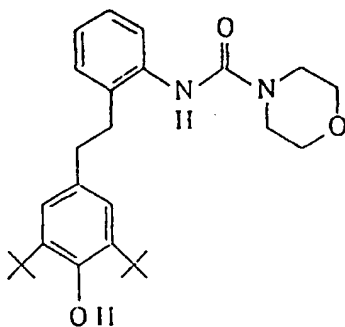
Example 122

4-[N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]carbamoyl]morpholine

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The title compound was prepared in a similar manner to that mentioned in Example 11, using morpholine instead of decylamine. m.p. 186-189°C

¹H-NMR(δ ppm, CDCl₃) 7.47(dd, J=8, 2Hz, 1H), 7.19-7.27(m, 2H), 7.14(ddd, J=7, 7, 2Hz, 1H), 6.78(s, 2H), 5.52(s, 1H), 5.09(s, 1H), 3.64(t, J=5Hz, 4H), 3.19(t, J=5Hz, 4H), 2.82(s, 4H), 1.36(s, 18H)

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IR(cm⁻¹) 3644, 3420, 3290, 2956, 1631, 1525, 1435, 1262, 1118, 756

Example 123

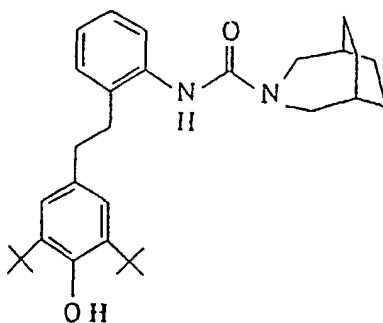
3-[N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]carbamoyl]-3-azabicyclo[3.2.2]nonane

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 3-azabicyclo[3.2.2]nonane instead of decylamine.

m.p. 184-186°C

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¹H-NMR(δ ppm, CDCl₃) 7.52(d, J=8Hz, 1H), 7.26-7.34(m, 2H), 7.09(dd, J=7, 7Hz, 1H), 6.81(s, 2H), 5.71(s, 1H), 5.08(s, 1H), 3.40(d, J=4Hz, 4H), 2.82(s, 4H), 1.96-2.04(m, 2H), 1.57-1.72(m, 8H), 1.37(s, 18H)
IR(cm⁻¹) 3630, 3430, 3334, 2930, 2860, 1627, 1511, 754

55

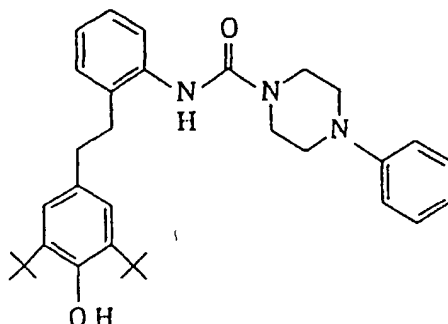
Example 124

1-[N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]carbamoyl]-4-phenylpiperazine

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 1-phenylpiperazine instead of decylamine. m.p. 155-156°C

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$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.11-7.48(m, 6H), 6.88-6.92(m, 1H), 6.89(d, $J=8\text{Hz}$, 2H), 6.79(s, 2H), 5.61(t, $J=5\text{Hz}$, 4H), 3.12(t, $J=5\text{Hz}$, 4H), 2.83(s, 4H), 1.37(s, 18H)
 $\text{IR}(\text{cm}^{-1})$ 3584, 3372, 2960, 1639, 1601, 1505, 1435, 1234, 999, 753

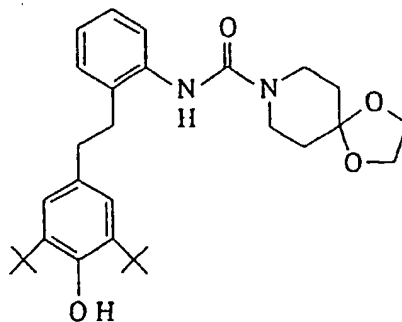
Example 125

8-[N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]carbamoyl]-1,4-dioxo-8-azaspiro[4.5]decane

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 1,4-dioxo-8-azaspiro[4.5]decane instead of decylamine. m.p. 163-164°C

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$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.45(d, $J=7\text{Hz}$, 1H), 7.17-7.26(m, 2H), 7.12(dd, $J=7, 7\text{Hz}$, 1H), 6.78(s, 2H), 5.59(bs, 1H), 5.09(s, 1H), 3.96(s, 4H), 3.30(t, $J=6\text{Hz}$, 4H), 2.82(s, 4H), 1.65(t, $J=6\text{Hz}$, 4H), 1.36(s, 18H)
 $\text{IR}(\text{cm}^{-1})$ 3430, 3300, 2955, 1645, 1510, 1490, 1455, 1440, 1250, 1120, 950, 750

55

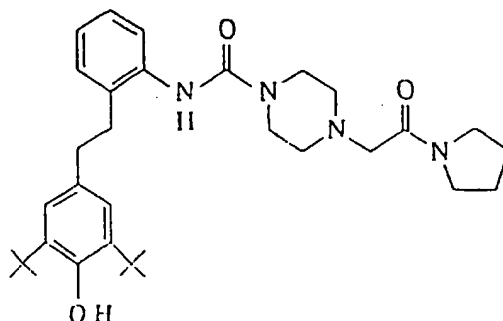
Example 126

1-[N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]carbamoyl]-4-(1-pyrrolidinylcarbonylmethyl)piperazine

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20 The title compound was prepared in a similar manner to that mentioned in Example 11, using 1-(1-pyrrolidinylcarbonylmethyl)piperazine instead of decylamine.
m.p. 212-214°C

25 ¹H-NMR(δ ppm, CDCl₃) 7.47(d, J=8Hz, 1H), 7.16-7.25(m, 2H), 7.11(ddd, J=7, 7, 1Hz, 1H), 6.78(s, 2H), 5.59(s, 1H), 5.10(s, 1H), 3.45-3.52(m, 4H), 3.28(t, J=5Hz, 4H), 3.11(s, 2H), 2.81(s, 4H), 2.50(t, J=5Hz, 4H), 1.80-2.00(m, 4H), 1.36(s, 18H)
IR(cm⁻¹) 3500, 3328, 2960, 1626, 1521, 1457, 1437, 750

Example 127

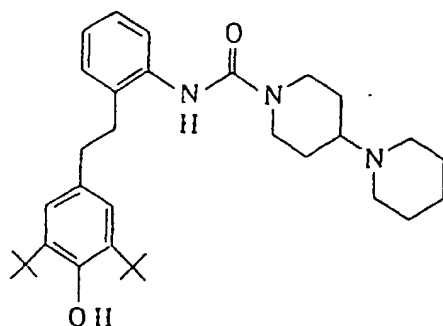
30

1-[N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]carbamoyl]-4-piperidinopiperidine

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50 The title compound was prepared in a similar manner to that mentioned in Example 11, using 4-piperidinopiperidine instead of decylamine. m.p. 64-67°C

55 ¹H-NMR(δ ppm, CDCl₃) 7.48(d, J=7Hz, 1H), 7.16-7.25(m, 2H), 7.11(ddd, J=7, 7, 2Hz, 1H), 6.79(s, 2H), 5.62(s, 1H), 5.09(s, 1H), 3.73-3.81(m, 2H), 2.81(s, 4H), 2.65-2.75(m, 2H), 2.44-2.51(m, 4H), 2.33-2.44(m, 1H), 1.75-1.82(m, 2H), 1.54-1.62(m, 4H), 1.39-1.50(m, 4H), 1.37(s, 18H)
IR(cm⁻¹) 3636, 3420, 2934, 1640, 1520, 1450, 1250, 750

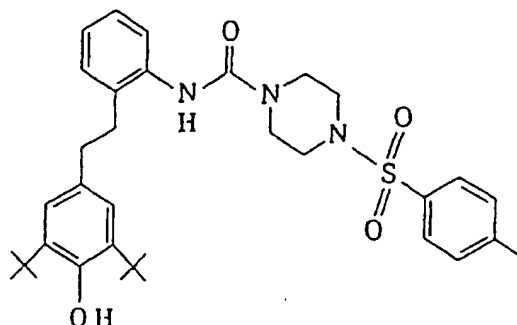
Example 128

1-[N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]carbamoyl]-4-(p-toluenesulfonyl)piperazine

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 1-(p-toluenesulfonyl)piperazine instead of decylamine.

m.p. 195-197°C

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$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.61(d, $J=8\text{Hz}$, 2H), 7.29-7.36(m, 3H), 7.19-7.24(m, 3H), 6.73(s, 2H), 5.41(bs, 1H), 5.12(s, 1H), 3.26(t, $J=5\text{Hz}$, 4H), 2.93(t, $J=5\text{Hz}$, 4H), 2.70-2.83(m, 4H), 2.45(s, 3H), 1.35(s, 18H)
 $\text{IR}(\text{cm}^{-1})$ 3630, 3410, 2950, 1635, 1625, 1350, 1170, 730

Example 129

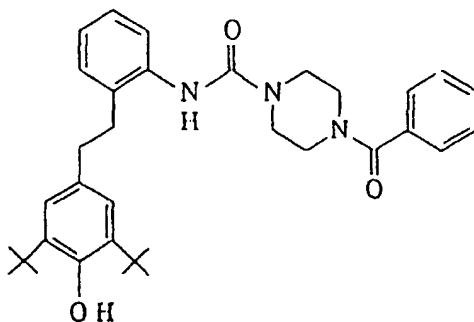
30

1-Benzoyl-4-[N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]carbamoyl]piperazine

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 1-benzoylpiperazine instead of decylamine. m.p. 207-209°C

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$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.37-7.48(m, 6H), 7.12-7.27(m, 3H), 6.76(s, 2H), 5.52(bs, 1H), 5.08(s, 1H), 3.12-3.85(m, 8H), 2.82(s, 4H), 1.33(s, 18H)
 $\text{IR}(\text{cm}^{-1})$ 3570, 3266, 2950, 1629, 1530, 1435, 1260, 1007, 754

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Example 130

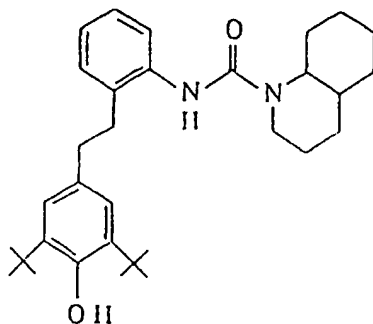
1-[N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]carbamoyl]decahydroquinoline

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The title compound was prepared in a similar manner to that mentioned in Example 11, using decahydroquinoline instead of decylamine.

$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.57(d, $J=8\text{Hz}$, 1H), 7.12-7.21(m, 2H), 7.07(dd, $J=7, 7\text{Hz}$, 1H), 6.86(s, 2H), 5.88(bs, 1H), 5.08(s, 1H), 4.06(m, 1H), 3.45(m, 1H), 2.75-2.90(m, 5H), 1.90(m, 1H), 1.63-1.80(m, 4H), 1.20-1.60(m, 8H), 1.39(m, 18H)

$\text{IR}(\text{cm}^{-1})$ 3430, 2924, 1632, 1510, 1434, 750

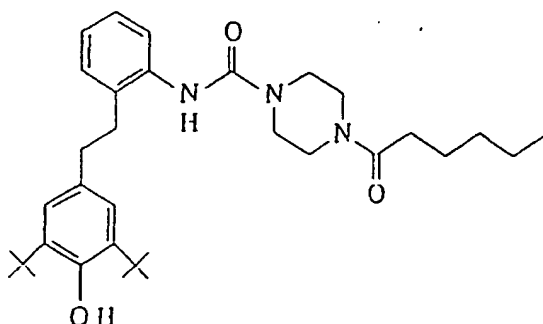
30 Example 131

1-[N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]carbamoyl]-4-pentanoylpiperazine

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 1-pentanoylpiperazine instead of decylamine. m.p. 126-128°C

$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.44(d, $J=9\text{Hz}$, 1H), 7.12-7.27(m, 3H), 6.77(s, 2H), 5.52(bs, 1H), 5.12(s, 1H), 3.56-3.63(m, 2H), 3.40-3.46(m, 2H), 3.27-3.34(m, 2H), 3.08-3.14(m, 2H), 2.82(s, 4H), 2.30(t, $J=5\text{Hz}$, 2H), 1.58-1.67(m, 2H), 1.36(s, 18H), 1.28-1.38(m, 4H)

$\text{IR}(\text{cm}^{-1})$ 3300, 2952, 1636, 1530, 1435, 1240, 994, 755

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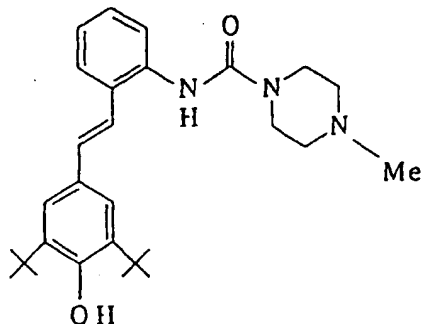
Example 132

1-[N-[2-(3,5-di-tert-butyl-4-hydroxystyryl)phenyl]carbamoyl]-4-methylpiperazine

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The title compound was prepared in a similar manner to that mentioned in Example 101, using 1-methylpiperazine instead of 2-(aminomethyl)pyridine. m.p. 192-194°C

25

$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.65(d, $J=8\text{Hz}$, 1H), 7.46-7.50(m, 1H), 7.33(s, 2H), 7.20-7.26(m, 1H), 7.11(dd, $J=9$, 1Hz, 1H), 6.99(d, $J=16\text{Hz}$, 1H), 6.94(d, $J=16\text{Hz}$, 1H), 6.39(bs, 1H), 5.34(s, 1H), 3.51(t, $J=5\text{Hz}$, 4H), 2.43(t, $J=5\text{Hz}$, 4H), 2.32(m, 3H), 1.47(s, 18H)
 $\text{IR}(\text{cm}^{-1})$ 3636, 3420, 3288, 2952, 1635, 1525, 1485, 1439, 1236, 1149, 959, 765, 755

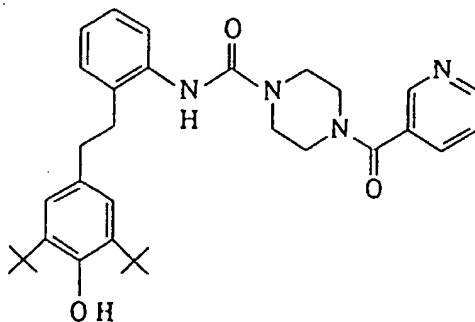
30 Example 133

1-[N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]carbamoyl]-4-nicotinoylpiperazine

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 1-nicotinoylpiperazine instead of decylamine. m.p. 171-172°C

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$^1\text{H-NMR}$ (δ ppm, CDCl_3) 8.70(dd, $J=5$, 2Hz, 1H), 8.66(d, $J=1\text{Hz}$, 1H), 7.75(ddd, $J=8$, 8, 2Hz, 1H), 7.36-7.42(m, 2H), 7.14-7.27(m, 3H), 6.75(s, 2H), 5.52(s, 1H), 5.11(s, 1H), 3.10-3.80(m, 8H), 2.82(s, 4H), 1.33(s, 18)
 $\text{IR}(\text{cm}^{-1})$ 3636, 3420, 3288, 2952, 1635, 1525, 1485, 1439, 1236, 1149, 959, 765, 755

Example 134

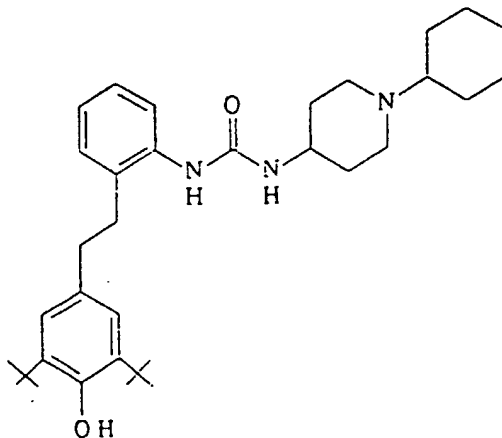
N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(1-cyclohexyl-4-piperidyl)urea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 4-amino-1-cyclohex-

25 ylpiperidine instead of decylamine.

$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.15-7.25(m, 4H), 6.79(s, 2H), 5.38(bs, 2H), 5.12(s, 1H), 4.55(bs, 1H), 3.65-3.75(m, 1H),
2.90-2.98(m, 2H), 2.75-2.90(m, 4H), 2.35-2.45(m, 3H), 1.85-2.00(m, 4H), 1.78(bs, 2H), 1.45-1.65(m, 3H), 1.38(s,
18H), 1.00-1.35(m, 5H)

30 $\text{IR}(\text{cm}^{-1})$ 3638, 3262, 1658, 1643, 1560, 1542, 1435, 1233, 754

Example 135

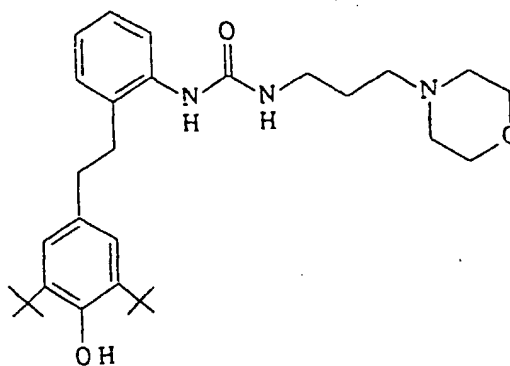
N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(3-morpholinopropyl)urea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 4-(3-aminopro-

55 pyl)morpholine instead of decylamine. m.p. 138-139°C

$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.19-7.29(m, 4H), 6.80(s, 2H), 5.19(bs, 1H), 5.12(s, 1H), 5.04(t, J=5Hz, 1H), 3.44(bs, 4H),
3.25(q, J=6Hz, 2H), 2.77-2.87(m, 4H), 2.25-2.35(m, 6H), 1.60(quint., J=7Hz, 2H), 1.38(s, 18H)
 $\text{IR}(\text{cm}^{-1})$ 3528, 3304, 1633, 1565, 1436, 1238, 1116, 872, 752

Example 136

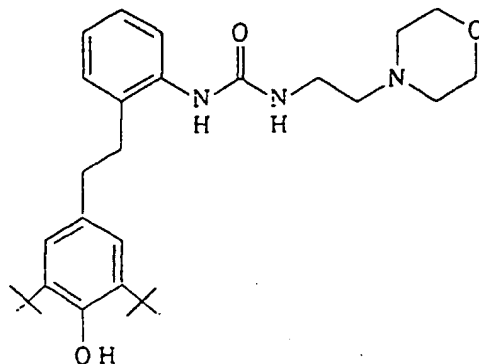
N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(2-morpholinoethyl)urea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 4-(2-aminoethyl)morpholine instead of decylamine. m.p. 166-167°C

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$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.19-7.28(m, 4H), 6.80(s, 2H), 5.19(s, 1H), 5.14(s, 1H), 4.91(s, 1H), 3.56(t, J=6Hz, 4H), 3.24(t, J=6Hz, 2H), 2.75-2.89(m, 4H), 2.30-2.42(m, 6H), 1.38(s, 18H)
 $\text{IR}(\text{cm}^{-1})$ 3566, 3326, 1643, 1574, 1436, 1300, 1238, 1116, 755

Example 137

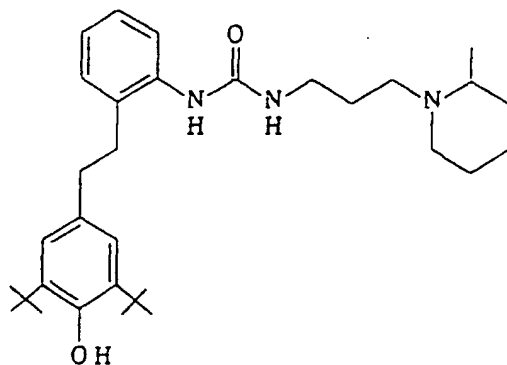
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N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(3-(2-methyl-1-piperidyl)propyl)urea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 1-(3-aminopropyl)-2-methylpiperidine instead of decylamine.

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$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.14-7.30(m, 4H), 6.81(s, 2H), 5.43(bs, 1H), 5.36(bs, 1H), 5.11(s, 1H), 3.15-3.30(m, 2H), 2.70-2.87(m, 6H), 2.20-2.30(m, 2H), 2.01(t, J=10Hz, 1H), 1.40-1.65(m, 5H), 1.38(s, 18H), 1.00-1.40(m, 3H), 0.98(d, J=6Hz, 3H)
 $\text{IR}(\text{cm}^{-1})$ 3638, 3294, 1643, 1543, 1436, 1234, 754

Example 138

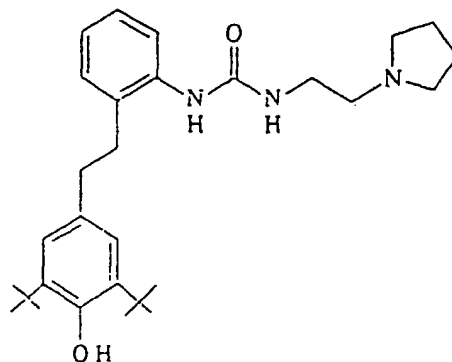
N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-[2-(1-pyrrolidiny)ethyl]urea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 1-(2-aminoethyl)pyrrolidine instead of decylamine.

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$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.37(d, $J=7\text{Hz}$, 1H), 7.11-7.21(m, 3H), 6.82(s, 2H), 5.55(bs, 1H), 5.26(s, 1H), 5.03(s, 1H), 3.29(t, $J=6\text{Hz}$, 2H), 2.65-2.85(m, 5H), 2.59(t, $J=6\text{Hz}$, 2H), 2.53(bs, 3H), 1.74(bs, 4H), 1.38(s, 18H)
 $\text{IR}(\text{cm}^{-1})$ 3638, 3350, 1686, 1546, 1436, 1234, 753

30 Example 139

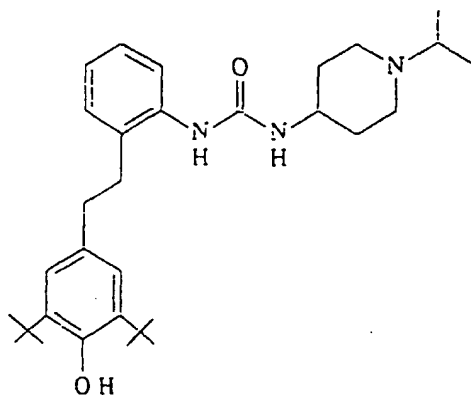
N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-[1-(2-propyl)-4-piperidyl]urea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 4-amino-1-(2-propyl)piperidine instead of decylamine. m.p. 191-193°C

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$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.15-7.26(m, 4H), 6.78(s, 2H), 5.11(bs, 2H), 4.30(bs, 1H), 3.59-3.72(m, 1H), 2.73-2.90(m, 7H), 2.25-2.37(m, 2H), 1.87-1.98(m, 2H), 1.30-1.50(m, 2H), 1.38(s, 18H), 1.07(d, $J=6\text{Hz}$, 6H)
 $\text{IR}(\text{cm}^{-1})$ 3358, 2948, 1641, 1561, 1435, 1235

Example 140

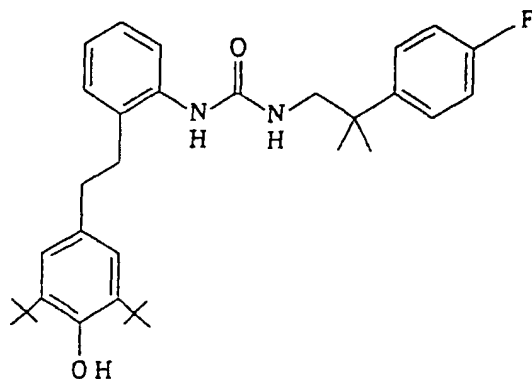
N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-[2-(4-fluorophenyl)-2-methylpropyl]urea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 4-fluoro- β,β -dimethylphenethylamine instead of decylamine. m.p. 179-180°C

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$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.14-7.20(m, 4H), 7.08(t, $J=7\text{Hz}$, 1H), 6.87-6.96(m, 3H), 6.74(s, 2H), 5.08(s, 1H), 5.00(s, 1H), 3.95-4.05(m, 1H), 3.30(d, $J=6\text{Hz}$, 2H), 2.70-2.80(m, 4H), 1.36(s, 18H), 1.24(s, 6H)
 $\text{IR}(\text{cm}^{-1})$ 3638, 3370, 1644, 1653, 1613, 1436, 1231, 1166, 833, 762

30 Example 141

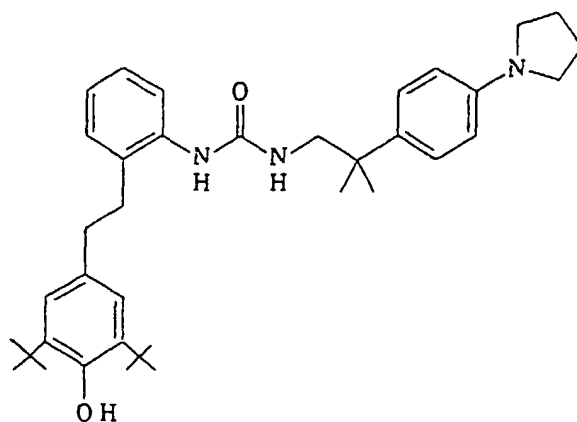
N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-[2-[4-(1-pyrrolidinyl)phenyl]-2-methylpropyl]urea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 1-[4-(1-amino-2-methyl-2-propyl)phenyl]pyrrolidine instead of decylamine.

55 m.p. 195-196°C

$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.02-7.18(m, 6H), 6.77(s, 2H), 6.43(d, $J=9\text{Hz}$, 2H), 5.08(s, 2H), 4.14(t, $J=6\text{Hz}$, 1H), 3.28(t, $J=6\text{Hz}$, 2H), 3.22-3.25(m, 4H), 2.70-2.78(m, 4H), 1.97-2.01(m, 4H), 1.37(s, 18H), 1.23(s, 6H)
 $\text{IR}(\text{cm}^{-1})$ 3642, 3354, 1642, 1615, 1562, 1524, 1369, 1234, 814, 750

Example 142

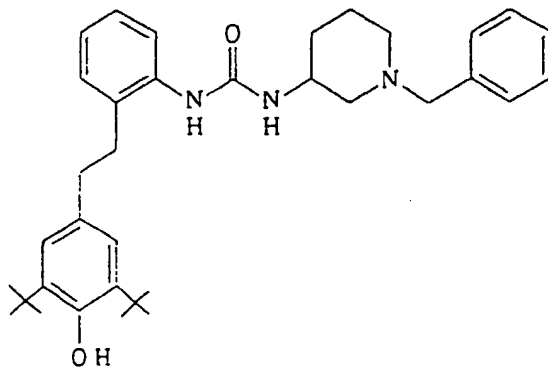
N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(1-benzyl-3-piperidyl)urea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 3-amino-1-benzyl-piperidine instead of decylamine.

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$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.20-7.40(m, 9H), 6.79(s, 2H), 5.12(bs, 1H), 5.09(s, 1H), 3.87-3.96(m, 1H), 3.49(bs, 1H), 3.37(d, $J=13\text{Hz}$, 1H), 3.28(d, $J=13\text{Hz}$, 1H), 2.70-2.90(m, 4H), 2.40-2.50(m, 2H), 1.30-1.70(m, 24H)
 $\text{IR}(\text{cm}^{-1})$ 3632, 3338, 2948, 1639, 1542, 1435, 1234, 744, 699

30 Example 143

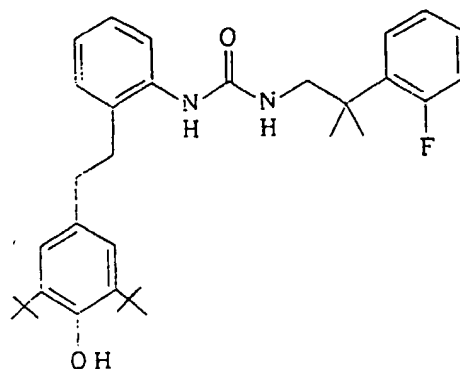
N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-[2-(2-fluorophenyl)-2-methylpropyl]urea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 2-fluoro- β,β -dimethylphenethylamine instead of decylamine. m.p. 182-183°C

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$^1\text{H-NMR}$ (δ ppm, CDCl_3) 6.88-7.21(m, 8H), 6.75(s, 2H), 5.07(s, 1H), 5.02(s, 1H), 4.02-4.09(m, 1H), 3.50(d, $J=6\text{Hz}$, 2H), 2.67-2.78(m, 4H), 1.36(s, 18H), 1.33(s, 6H)
 $\text{IR}(\text{cm}^{-1})$ 3650, 3330, 2960, 1640, 1575, 1445, 1255, 765

Example 144

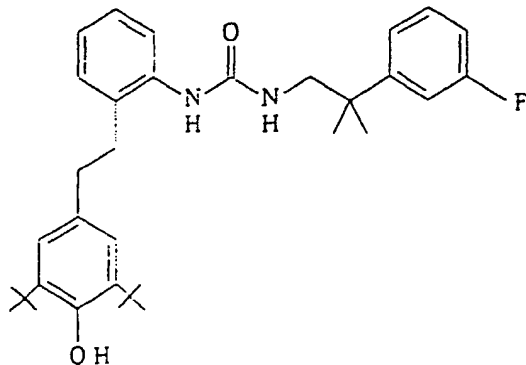
N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-[2-(3-fluorophenyl)-2-methylpropyl]urea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 3-fluoro- β,β -dimethylphenethylamine instead of decylamine. m.p. 165-166°C

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$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.04-7.23(m, 4H), 6.80-7.00(m, 4H), 6.74(s, 2H), 5.08(s, 1H), 4.94(s, 1H), 3.98(t, J=6Hz, 1H), 3.32(d, J=6Hz, 2H), 2.68-2.79(m, 4H), 1.36(s, 18H), 1.25(s, 6H)

$\text{IR}(\text{cm}^{-1})$ 3640, 3350, 2970, 1645, 1615, 1590, 1560, 1440, 910, 765, 700

30 Example 145

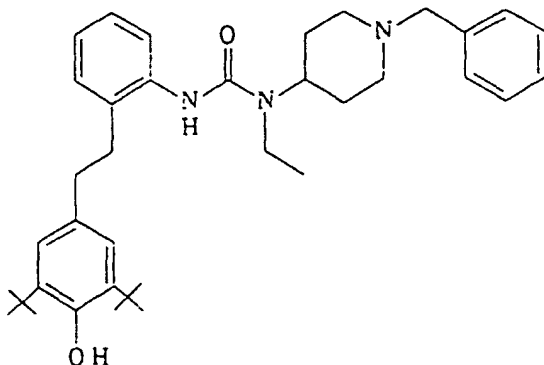
N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(1-benzyl-4-piperidyl)-N'-ethylurea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 4-ethylamino-1-benzylpiperidine instead of decylamine. m.p. 149-151°C

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$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.72(d, J=8Hz, 1H), 7.15-7.33(m, 7H), 7.07(t, J=7Hz, 1H), 6.83(s, 2H), 5.91(bs, 1H), 5.07(s, 1H), 4.16-4.38(m, 1H), 3.48(s, 2H), 3.02(q, J=7Hz, 2H), 2.93(d, J=12Hz, 2H), 2.82(bs, 4H), 2.03-2.10(m, 2H), 1.60-1.75(m, 4H), 1.37(s, 18H), 1.16(t, J=7Hz, 3H)

$\text{IR}(\text{cm}^{-1})$ 3334, 2954, 1631, 1520, 1502, 1263, 1202, 743

Example 146

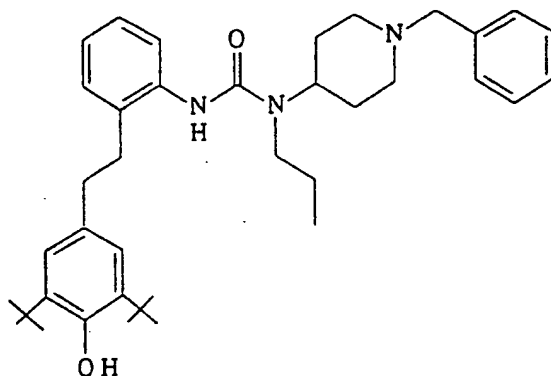
N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(1-benzyl-4-piperidyl)-N'-propylurea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 1-benzyl-4-propylaminopiperidine instead of decylamine.

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$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.76(d, $J=7\text{Hz}$, 1H), 7.10-7.35(m, 7H), 7.04(td, $J=6$, 1Hz, 1H), 6.87(s, 2H), 6.07(bs, 1H), 5.06(s, 1H), 4.12-4.23(m, 1H), 3.48(s, 2H), 3.04(bt, $J=8\text{Hz}$, 2H), 2.94(d, $J=12\text{Hz}$, 2H), 2.81(s, 4H), 2.00-2.10(m, 2H), 1.50-1.75(m, 6H), 1.39(s, 18H), 0.86(t, $J=7\text{Hz}$, 3H)
 $\text{IR}(\text{cm}^{-1})$ 3634, 3450, 2956, 1650, 1509, 1451, 1234, 742

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Example 147

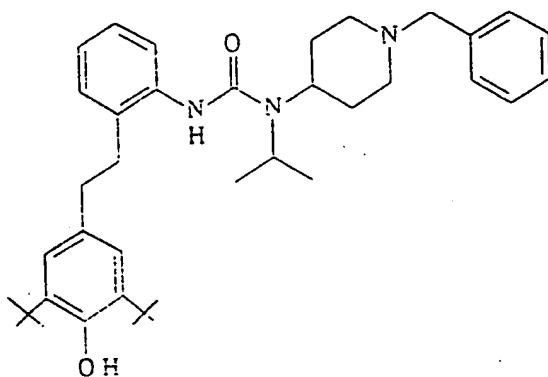
N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(1-benzyl-4-piperidyl)-N'-(2-propyl)urea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 1-benzyl-4-[(2-propyl)amino]piperidine instead of decylamine.

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$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.65(d, $J=8\text{Hz}$, 1H), 7.10-7.30(m, 7H), 7.04(td, $J=7$, 1Hz, 1H), 6.89(s, 2H), 6.03(bs, 1H), 5.05(s, 1H), 3.70-3.90(m, 2H), 3.47(s, 2H), 2.75-2.98(m, 6H), 1.90-2.05(m, 4H), 1.55-1.70(m, 2H), 1.39(s, 18H), 1.31(d, $J=7\text{Hz}$, 6H)
 $\text{IR}(\text{cm}^{-1})$ 3450, 2954, 1650, 1521, 1451, 1237, 744

Example 148

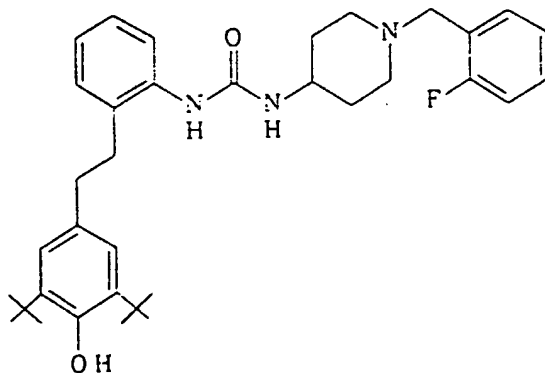
N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-[1-(2-fluorobenzyl)-4-piperidyl]urea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 4-amino-1-(2-fluorobenzyl)piperidine instead of decylamine.

25 m.p. 136-137°C

$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.14-7.34(m, 6H), 6.95-7.10(m, 2H), 6.77(s, 2H), 5.10(s, 1H), 4.99(s, 1H), 4.10(d, $J=8\text{Hz}$, 1H), 3.55-3.71(m, 1H), 3.52(s, 2H), 2.68-2.88(m, 6H), 2.07-2.17(m, 2H), 1.82-1.90(m, 2H), 1.37(s, 18H), 1.24-1.35(m, 2H)

30 IR(cm^{-1}) 3640, 3340, 2960, 1650, 1590, 1570, 1495, 1235, 765

Example 149

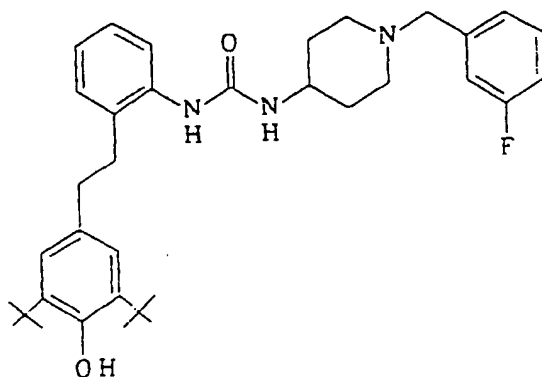
N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-[1-(3-fluorobenzyl)-4-piperidyl]urea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 4-amino-1-(3-fluorobenzyl)piperidine instead of decylamine. m.p. 99-100°C

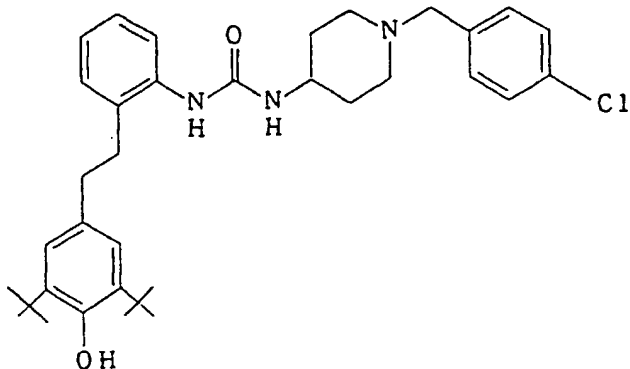
$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.15-7.27(m, 5H), 7.67-7.04(m, 2H), 6.86-6.94(m, 1H), 5.10(s, 1H), 4.12(d, $J=8\text{Hz}$, 1H), 3.57-3.70(m, 1H), 3.42(s, 2H), 2.66-2.86(m, 6H), 2.06(t, $J=12\text{Hz}$, 2H), 1.86(d, $J=12\text{Hz}$, 2H), 1.38(s, 18H), 1.24-

1.35(m, 2H)

IR(cm^{-1}) 3635, 3340, 2950, 1640, 1590, 1565, 1490, 1440, 1235, 880, 750, 690

Example 150

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-[1-(4-chlorobenzyl)-4-piperidyl]urea



The title compound was prepared in a similar manner to that mentioned in Example 11, using 4-amino-1-(4-chlorobenzyl)piperidine instead of decylamine.

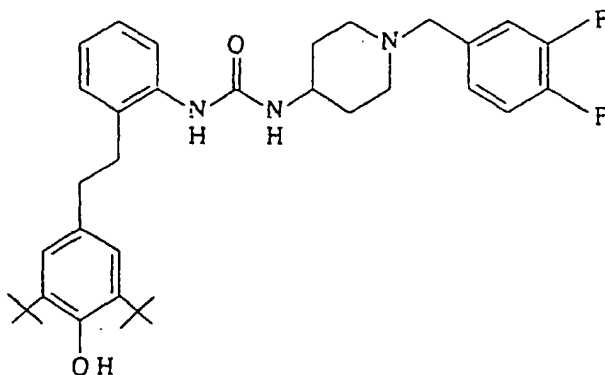
m.p. 184-185°C

$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.15-7.32(m, 8H), 6.77(s, 2H), 5.10(s, 1H), 4.98(s, 1H), 4.09(d, $J=8\text{Hz}$, 1H), 3.57-3.70(m, 1H), 3.39(s, 2H), 2.74-2.87(m, 4H), 2.69(d, $J=11\text{Hz}$, 2H), 2.04(t, $J=11\text{Hz}$, 2H), 1.81-1.88(m, 2H), 1.37(s, 18H), 1.14-1.22(m, 2H)

IR(cm^{-1}) 3645, 3360, 2940, 1640, 1590, 1555, 1490, 1435, 1295, 1235, 1095, 750

Example 151

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-[1-(3,4-difluorobenzyl)-4-piperidyl]urea



The title compound was prepared in a similar manner to that mentioned in Example 11, using 4-amino-1-(3,4-difluorobenzyl)piperidine instead of decylamine.

m.p. 155-156°C

EP 0 625 507 B1

$^1\text{H-NMR}$ (δ ppm, CDCl_3) 6.92-7.28(m, 7H), 6.77(s, 2H), 5.10(s, 1H), 4.97(s, 1H), 4.08(d, $J=8\text{Hz}$, 1H), 3.58-3.72(m, 1H), 3.37(s, 2H), 2.74-2.87(m, 4H), 2.05(t, $J=11\text{Hz}$, 2H), 1.82-1.90(m, 2H), 1.38(s, 18H), 1.24-1.35(m, 2H)
 $\text{IR}(\text{cm}^{-1})$ 3650, 3370, 2965, 1645, 1570, 1525, 1440, 1295, 1240, 885, 785, 765

5 Example 152

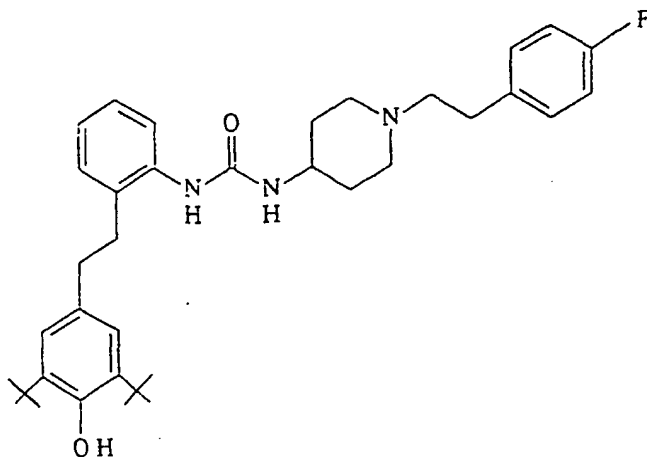
N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-[1-(4-fluorophenethyl)-4-piperidyl]urea

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30 The title compound was prepared in a similar manner to that mentioned in Example 11, using 4-amino-1-(4-fluorophenethyl)piperidine instead of decylamine.
m.p. 117-119°C

35 $^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.10-7.20(m, 6H), 6.94(td, $J=7, 2\text{Hz}$, 2H), 6.78(s, 2H), 5.11(s, 1H), 5.04(bs, 1H), 4.13(bd, $J=8\text{Hz}$, 1H), 3.58-3.70(m, 1H), 2.70-2.90(m, 8H), 2.45-2.55(m, 2H), 2.08-2.12(m, 2H), 1.85-1.95(m, 2H), 1.30-1.40(m, 2H), 1.38(s, 18H)
 $\text{IR}(\text{cm}^{-1})$ 3630, 3314, 2948, 1634, 1565, 1510, 1228, 748

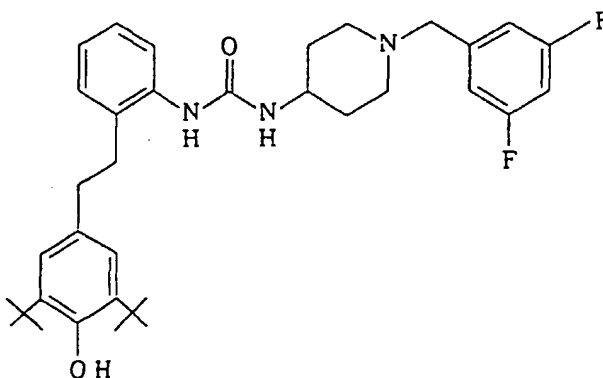
40 Example 153

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N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-[1-(3,5-difluorobenzyl)-4-piperidyl]urea

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EP 0 625 507 B1

The title compound was prepared in a similar manner to that mentioned in Example 11, using 4-amino-1-(3,5-difluorobenzyl)piperidine instead of decylamine.

m.p. 119-120°C

5 $^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.17-7.28(m, 4H), 6.82(d, $J=6\text{Hz}$, 2H), 6.77(s, 2H), 6.62-6.69(m, 1H), 5.11(s, 1H), 4.97(s, 1H), 4.09(d, $J=8\text{Hz}$, 1H), 3.58-3.71(m, 1H), 3.40(s, 2H), 2.66-2.88(m, 6H), 2.07(t, $J=11\text{Hz}$, 2H), 1.83-1.92(m, 2H), 1.38(s, 18H), 1.25-1.36(m, 2H)
IR(cm^{-1}) 3640, 3350, 2960, 1635, 1605, 1505, 1440, 1325, 1235, 1120, 995, 855

10 Example 154

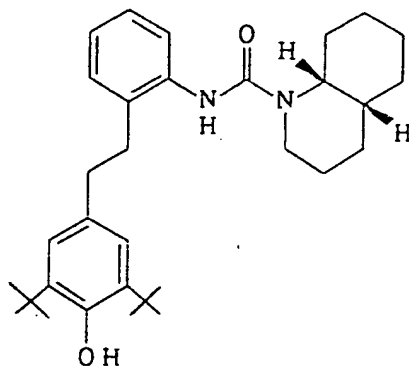
2-[N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]carbamoyl]-cis-decahydroquinoline

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The title compound was prepared in a similar manner to that mentioned in Example 11, using cis-decahydroquinoline instead of decylamine. m.p. 132-133°C

35 $^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.64(d, $J=8\text{Hz}$, 1H), 7.23-7.30(m, 2H), 7.11(t, $J=7\text{Hz}$, 1H), 6.93(s, 2H), 5.94(s, 1H), 5.14(s, 1H), 4.09-4.20(m, 1H), 3.48-3.59(m, 1H), 2.83-2.94(m, 5H), 1.50-2.00(m, 9H), 1.45(s, 18H), 1.24-1.42(m, 4H)
IR(cm^{-1}) 3640, 3320, 2925, 2860, 1630, 1515, 1435, 1360, 1275, 1235, 1160, 755

40 Example 155

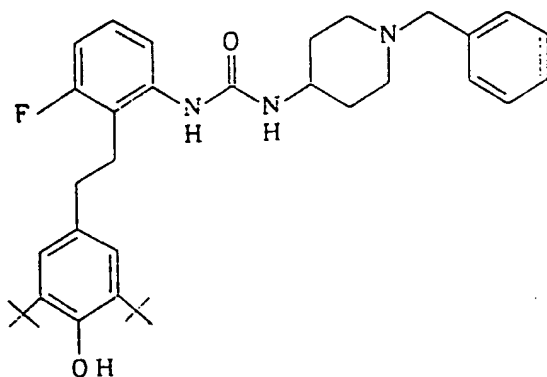
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N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)-3-fluorophenyl]-N'-(1-benzyl-4-piperidyl)urea

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EP 0 625 507 B1

The title compound was prepared in a similar manner to that mentioned in Example 108, using 4-(2-amino-6-fluorophenethyl)-2,6-di-tert-butylphenol instead of 4-(2-amino-3,5-difluorophenethyl)-2,6-di-tert-butylphenol.
m.p. 103-105°C

5 $^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.20-7.35(m, 5H), 7.13(t, $J=8\text{Hz}$, 1H), 7.03(d, $J=8\text{Hz}$, 1H), 6.93(t, $J=9\text{Hz}$, 1H), 6.75(s, 2H), 5.13(s, 1H), 4.60(bs, 1H), 3.95(bd, $J=8\text{Hz}$, 1H), 3.54-3.66(m, 1H), 3.44(s, 2H), 2.70-2.90(m, 6H), 2.00-2.10(m, 2H), 1.80-1.90(m, 2H), 1.30-1.40(m, 2H), 1.36(s, 18H)
 $\text{IR}(\text{cm}^{-1})$ 3630, 3300, 2948, 1632, 1565, 1452, 1235, 699

10 Example 156

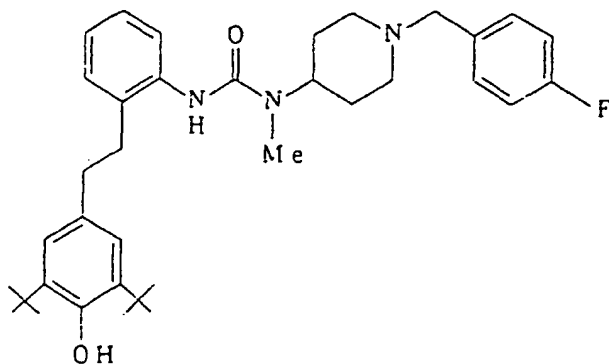
N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-[1-(4-fluorobenzyl)-4-piperidyl]-N'-methylurea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 1-(4-fluorobenzyl)-4-(methylamino)piperidine instead of decylamine. m.p. 177-178°C

35 $^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.63(d, $J=8\text{Hz}$, 1H), 7.17-7.28(m, 4H), 7.08-7.13(m, 1H), 6.95-7.03(m, 2H), 6.78(s, 2H), 5.61(s, 1H), 5.08(s, 1H), 4.17-4.28(m, 1H), 3.43(s, 2H), 2.90(d, $J=12\text{Hz}$, 2H), 2.81(s, 4H), 2.50(s, 3H), 1.98-2.07(m, 2H), 1.54-1.68(m, 4H), 1.35(s, 18H)
 $\text{IR}(\text{cm}^{-1})$ 3630, 3330, 2970, 1635, 1520, 1440, 1330, 1230, 1050, 760,

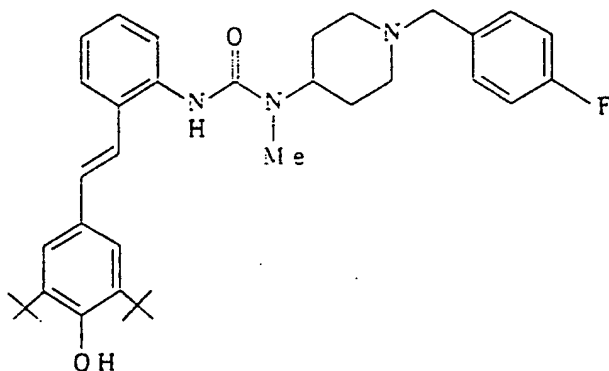
40 Example 157

N-[2-(3,5-di-tert-butyl-4-hydroxystyryl)phenyl]-N'-[1-(4-fluorobenzyl)-4-piperidyl]-N'-methylurea

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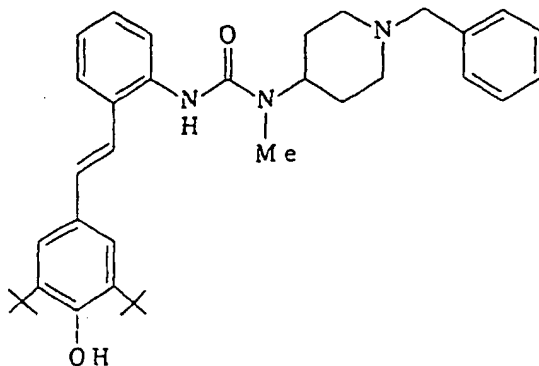
EP 0 625 507 B1

The title compound was prepared in a similar manner to that mentioned in Example 101, using 1-(4-fluorobenzyl)-4-(methylamino)piperidine instead of 2-(aminomethyl)pyridine. m.p. 174-175°C

¹H-NMR(δ ppm, CDCl₃) 7.79(d, J=8Hz, 1H), 7.45(dd, J=7, 1Hz, 1H), 7.31(s, 2H), 7.20-7.30(m, 3H), 7.05-7.13(m, 1H), 6.93-7.03(m, 4H), 6.38(s, 1H), 5.32(s, 1H), 4.14-4.26(m, 1H), 3.46(s, 2H), 2.85-2.96(m, 5H), 1.99-2.10(m, 2H), 1.63-1.82(m, 4H), 1.46(s, 18H)
IR(cm⁻¹) 3640, 3450, 2960, 1640, 1510, 1225, 1160, 1045, 965, 760

Example 158

N-[2-(3,5-di-tert-butyl-4-hydroxystyryl)phenyl]-N'-(1-benzyl-4-piperidyl)-N'-methylurea

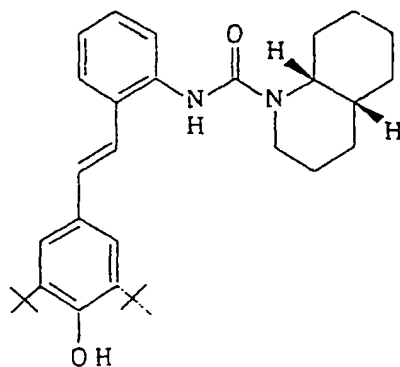


The title compound was prepared in a similar manner to that mentioned in Example 101, using 1-benzyl-4-(methylamino)piperidine instead of 2-(aminomethyl)pyridine.
m.p. 163-164°C

¹H-NMR(δ ppm, CDCl₃) 7.78(d, J=7Hz, 1H), 7.45(dd, J=8, 1Hz, 1H), 7.20-7.35(m, 8H), 7.04-7.12(m, 1H), 7.00(d, J=16Hz, 1H), 6.93(d, J=16Hz, 1H), 6.38(s, 1H), 5.32(s, 1H), 4.14-4.27(m, 1H), 3.48(s, 2H), 2.94(d, J=12Hz, 2H), 2.90(s, 3H), 2.00-2.11(m, 2H), 1.60-1.84(m, 4H), 1.46(s, 18H)
IR(cm⁻¹) 3625, 3440, 3260, 2960, 1635, 1530, 1485, 1240, 1150, 1045, 960, 755, 745, 700

Example 159

2-[N-[2-(3,5-di-tert-butyl-4-hydroxystyryl)phenyl]carbamoyl]-cis-decahydroquinoline



EP 0 625 507 B1

The title compound was prepared in a similar manner to that mentioned in Example 101, using cis-decahydroquinoline instead of 2-(aminomethyl)pyridine.

¹H-NMR(δ ppm, CDCl₃) 7.71(d, J=8Hz, 1H), 7.46(d, J=6Hz, 1H), 7.33(s, 2H), 7.20-7.28(m, 1H), 7.05-7.11(m, 1H),
5 7.00(d, J=16Hz, 1H), 6.93(d, J=16Hz, 1H), 6.41(s, 1H), 5.32(s, 1H), 3.85-4.07(m, 2H), 1.68-1.97(m, 5H), 1.47-
1.64(m, 5H), 1.47(s, 18H), 1.18-1.43(m, 3H)
¹IR(cm⁻¹) 3640, 3450, 3300, 2930, 2870, 1645, 1525, 1445, 1240, 1160, 965, 755

Example 160

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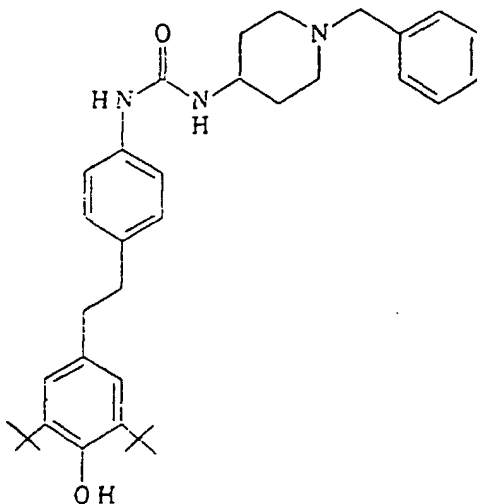
N-[4-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(1-benzyl-4-piperidyl)urea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 4-(4-aminophenethyl)-2,6-di-tert-butylphenol instead of 4-(2-aminophenethyl)-2,6-di-tert-butylphenol and using 4-amino-1-benzylpiperidine instead of decylamine. m.p. 195-197°C

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¹H-NMR(δ ppm, CDCl₃) 7.22-7.34(m, 5H), 7.15(s, 4H), 6.92(s, 2H), 6.10(s, 1H), 5.06(s, 1H), 4.56(d, J=8Hz, 1H),
3.66-3.78(m, 1H), 3.49(s, 2H), 2.75-2.90(m, 6H), 2.07-2.18(m, 2H), 1.91-1.99(m, 2H), 1.36-1.47(m, 2H), 1.43(s,
18H)
¹IR(cm⁻¹) 3620, 3378, 2946, 1659, 1604, 1542, 1515, 1435, 1324, 1234, 740

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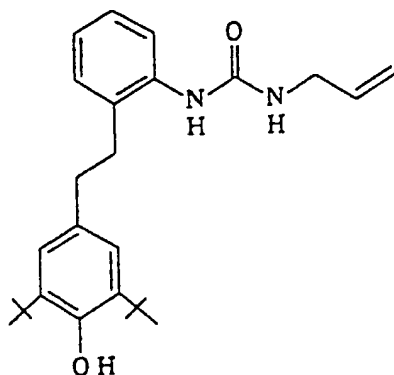
Example 161

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-allylurea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using allylamine instead of decylamine. m.p. 169-172°C

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$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.16-7.32(m, 5H), 6.78(s, 2H), 5.73-5.85(m, 1H), 4.96-5.14(m, 3H), 4.20-4.26(m, 1H), 3.73-3.80(m, 2H), 2.76-2.90(m, 4H), 1.37(s, 18H)
 $\text{IR}(\text{cm}^{-1})$ 3632, 3334, 2956, 1653, 1587, 1570, 1561, 1436, 1235, 924, 769

Example 162

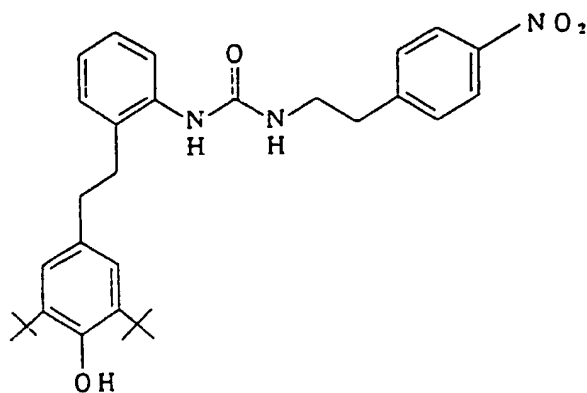
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N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(4-nitrophenethyl)urea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 4-nitrophenethylamine instead of decylamine. m.p. 134-136°C

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$^1\text{H-NMR}$ (δ ppm, CDCl_3) 8.08(d, $J=8\text{Hz}$, 1H), 7.10-7.29(m, 6H), 6.75(s, 2H), 5.12(s, 1H), 5.05(s, 1H), 4.28(t, $J=6\text{Hz}$, 1H), 3.39(td, $J=7, 6\text{Hz}$, 2H), 2.73-2.90(m, 6H), 1.35(s, 18H)
 $\text{IR}(\text{cm}^{-1})$ 3630, 3314, 2954, 1639, 1561, 1519, 1436, 1347, 753

Example 163

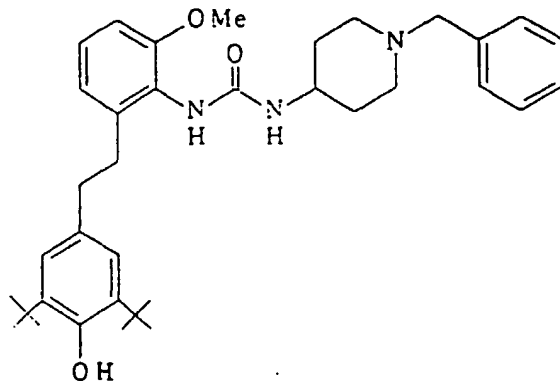
N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)-6-methoxyphenyl]-N'-(1-benzyl-4-piperidyl)urea

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The title compound was prepared in a similar manner to that mentioned in Example 108, using 4-(2-amino-3-methoxyphenethyl)-2,6-di-tert-butylphenol instead of 4-(2-amino-3,5-difluorophenethyl)-2,6-di-tert-butylphenol
m.p. 184-185°C

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$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.20-7.30(m, 6H), 6.88(d, $J=8\text{Hz}$, 1H), 6.80(s, 2H), 6.77(d, $J=8\text{Hz}$, 1H), 5.07(s, 1H), 4.88(s, 1H), 4.09(d, $J=8\text{Hz}$, 1H), 3.76(s, 3H), 3.60-3.70(m, 1H), 3.43(s, 2H), 2.86-2.90(m, 2H), 2.70-2.77(m, 4H), 2.05(t, $J=11\text{Hz}$, 2H), 1.86(d, $J=10\text{Hz}$, 2H), 1.38(s, 18H), 1.25(q, $J=10\text{Hz}$, 2H)
 $\text{IR}(\text{cm}^{-1})$ 3638, 3308, 1653, 1589, 1563, 1556, 1468, 1454, 1435, 1260, 1232, 738

Example 164

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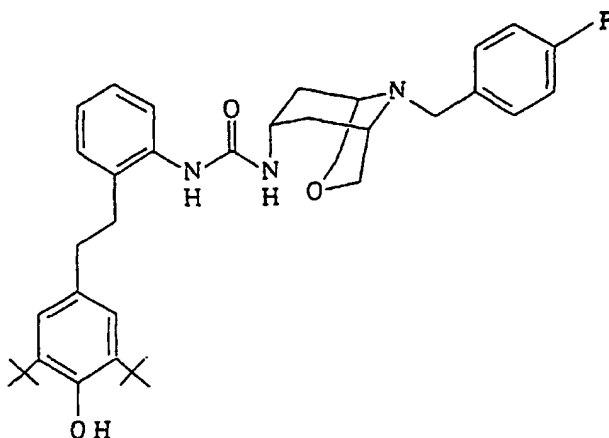
N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(endo-9-(4-fluorobenzyl)-3-oxa-9-azabicyclo[3.3.1]non-7-yl)urea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using endo-7-amino-9-(4-fluorobenzyl)-3-oxa-9-azabicyclo[3.3.1]nonane instead of decylamine.

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¹H-NMR(δ ppm, CDCl₃) 7.18-7.29(m, 6H), 7.06(d, J=11Hz, 1H), 6.99(d, J=9Hz, 1H), 6.96(d, J=9Hz, 1H), 6.83(s, 2H), 5.22(s, 1H), 5.09(s, 1H), 4.37(dd, J=17, 7Hz, 1H), 3.73(d, J=15Hz, 2H), 3.71(s, 2H), 3.39(d, J=11Hz, 2H), 2.84-2.87(m, 2H), 2.76-2.79(m, 2H), 2.52(s, 2H), 2.30-2.37(m, 2H), 1.39(s, 18H), 1.31-1.40(m, 2H)
 IR(cm⁻¹) 3636, 3324, 1652, 1525, 1511, 1506, 1436, 1223, 787, 759

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Example 165

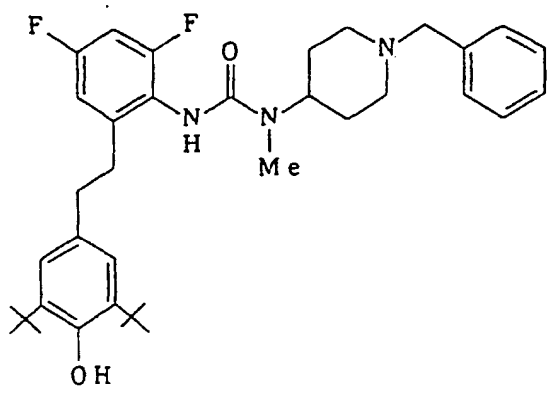
N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)-4,6-difluorophenyl]-N'-(1-benzyl-4-piperidyl)-N'-methylurea

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The title compound was prepared in a similar manner to that mentioned in Example 108, using 1-benzyl-4-(methylamino)piperidine instead of 4-amino-1-benzylpiperidine. m.p. 187-191°C

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¹H-NMR(δ ppm, CDCl₃) 7.20-7.40(m, 5H), 6.70-6.80(m, 4H), 5.09(s, 1H), 4.91(bs, 1H), 4.10-4.23(m, 1H), 3.47(s, 2H), 2.90-3.00(m, 2H), 2.80-2.90(m, 4H), 2.58(s, 3H), 2.00-2.10(m, 2H), 1.60-1.80(m, 4H), 1.36(s, 18H)
 IR(cm⁻¹) 3616, 3312, 1638, 1510, 1436, 1323, 1118

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Example 166

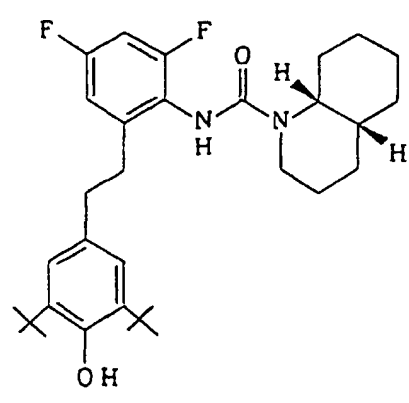
2-[N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)-4,6-difluorophenyl]carbamoyl]-cis-decahydroquinoline

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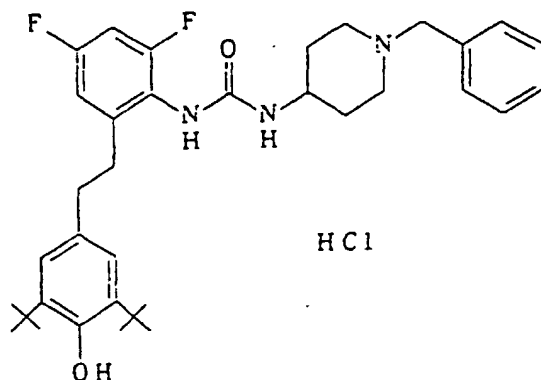
The title compound was prepared in a similar manner to that mentioned in Example 108, using cis-decahydroquinoline instead of 4-amino-1-benzylpiperidine.

m.p. 83-85°C

¹H-NMR(δ ppm, CDCl₃) 6.83(s, 2H), 6.70-6.80(m, 2H), 5.26(bs, 1H), 5.09(s, 1H), 4.05(bs, 1H), 3.49(bs, 2H), 2.70-2.90(m, 5H), 1.84-1.94(m, 1H), 1.65-1.80(m, 4H), 1.20-1.60(m, 8H), 1.39(s, 18H)
 IR(cm⁻¹) 3588, 3316, 2924, 1713, 1638, 1511, 1435, 1120

Example 167

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)-4,6-difluorophenyl]-N'-(1-benzyl-4-piperidyl)urea hydrochloride

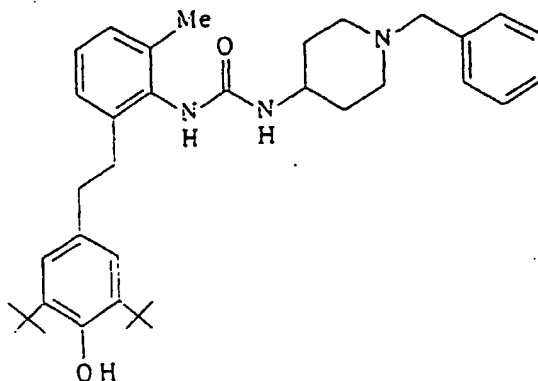


N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)-4,6-difluorophenyl]-N'-(1-benzyl-4-piperidyl)urea (1.15 g) was suspended in ethanol (20 ml) and heated at 50°C to dissolve it. To the solution was added 4N hydrochloric acid/ethyl acetate solution (anhydrous)(0.5 ml). This solution was concentrated to a volume of 5 ml, cooled to 0-5°C and allowed to stand for 4 hrs. The resultant crystals were filtered and dried to afford the title compound (1.00 g, 81%).
 m.p. 170-175°C

¹H-NMR(δ ppm, CDCl₃) 12.09(bs, 1H), 7.55(d, J=6Hz, 2H), 7.30-7.40(m, 3H), 6.84(s, 2H), 6.72(d, J=8Hz, 1H), 6.65(td, J=8, 2Hz, 1H), 5.10(s, 1H), 4.12(d, J=7Hz, 1H), 3.75-3.86(m, 1H), 3.35-3.40(m, 2H), 2.65-2.85(m, 6H), 2.10-2.25(m, 4H), 1.39(s, 18H)
 IR(cm⁻¹) 3430, 3300, 2952, 1680, 1554, 1436, 1236, 1122

Example 168

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)-6-methylphenyl]-N'-(1-benzyl-4-piperidyl)urea



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The title compound was prepared in a similar manner to that mentioned in Example 108, using 4-(2-amino-3-methylphenethyl)-2,6-di-tert-butylphenol instead of 4-(2-amino-3,5-difluorophenethyl)-2,6-di-tert-butylphenol.
m.p. 185-186°C

5 $^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.04-7.34(m, 8H), 6.78(s, 2H), 5.08(s, 1H), 4.83(s, 1H), 3.90(d, $J=8\text{Hz}$, 1H), 3.57-3.72(m, 1H), 3.42(s, 2H), 2.62-2.90(m, 6H), 2.19(s, 3H), 2.03(dd, $J=12, 11\text{Hz}$, 2H), 1.83(d, $J=11\text{Hz}$, 2H), 1.38(s, 18H), 1.16-1.32(m, 2H)
IR(cm^{-1}) 3638, 3324, 2950, 1639, 1555, 1436, 1233, 769, 734, 698

10 Example 169

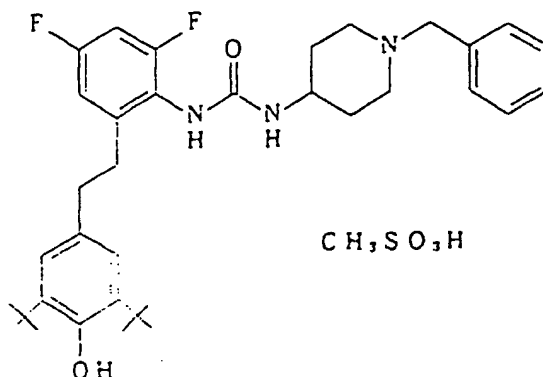
N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)-4,6-difluorophenyl]-N'-(1-benzyl-4-piperidyl)urea methanesulfonate

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N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)-4,6-difluorophenyl]-N'-(1-benzyl-4-piperidyl)urea (0.50 g) was suspended in ethanol (10 ml) and heated at 50°C to dissolve it. To the solution was added methanesulfonic acid (56 μl) and this solution was concentrated. The concentrate was dissolved with a mixed solvent of ethyl acetate (1 ml) and diisopropylether (3 ml). The solution was cooled to 0-5°C and allowed to stand overnight. The resultant crystals were filtered and dried to give the title compound (0.51 g, 87%).
m.p. 252-254°C

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$^1\text{H-NMR}$ (δ ppm, CDCl_3) 10.23(bs, 1H), 7.30-7.45(m, 5H), 6.80-6.92(m, 3H), 6.57-6.68(m, 1H), 5.10(s, 1H), 4.30(bs, 1H), 4.12(bs, 1H), 3.74-3.88(m, 1H), 3.40-3.50(m, 2H), 3.20-3.32(m, 1H), 2.60-2.80(m, 9H), 1.90-2.15(m, 4H), 1.39(s, 18H)
IR(cm^{-1}) 3262, 2954, 1657, 1562, 1438, 1220, 1163, 1119, 1041

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Example 170

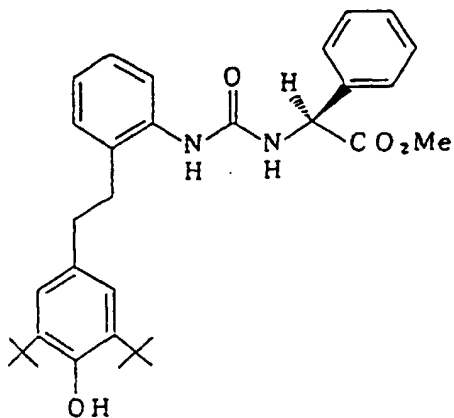
(S)-N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(α -methoxycarbonyl)benzylurea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using (S)- α -phenylglycine methyl ester instead of decylamine.
m.p. 145-150°C

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$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.170-7.34(m, 9H), 6.76(s, 2H), 5.51(d, J=8Hz, 1H), 5.23(d, J=7Hz, 1H), 5.13(s, 1H), 5.09(s, 1H), 3.68(s, 3H), 2.74-2.88(m, 4H), 1.35(s, 18H)
IR(cm^{-1}) 3644, 3345, 2944, 1752, 1644, 1546, 1436, 1211

Example 171

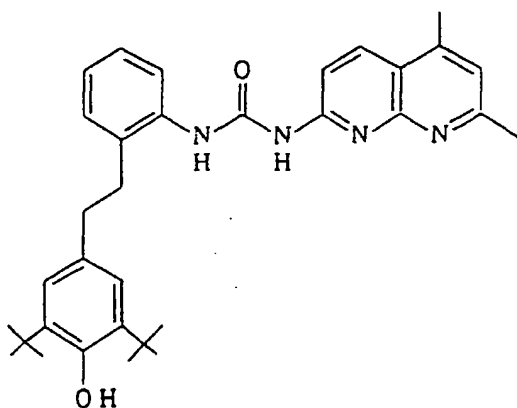
N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(2,4-dimethyl-1,8-naphthyridin-7-yl)urea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 7-amino-2,4-dimethyl-1,8-naphthyridine instead of decylamine.
m.p. 235-237°C

$^1\text{H-NMR}$ (δ ppm, CDCl_3) 8.22(d, J=9Hz, 1H), 7.86-7.96(m, 1H), 7.10-7.30(m, 3H), 7.02(s, 1H), 6.80(s, 2H), 4.93(s,

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1H), 3.15-3.27(m, 2H), 2.90-3.01(m, 2H), 2.62(s, 3H), 2.56(bs, 3H), 1.23(s, 18H)
IR(cm⁻¹) 3636, 2952, 1687, 1615, 1599, 1560, 1527, 1403, 1307, 751

Example 172

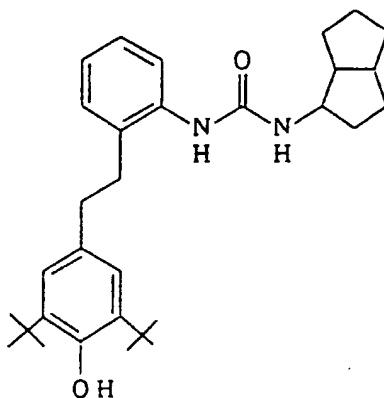
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N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(bicyclo[3.3.0]-2-octyl)urea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 1-aminobicyclo[3.3.0]octane instead of decylamine.

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¹H-NMR(δ ppm, CDCl₃) 7.14-7.29(m, 4H), 6.80(s, 2H), 5.11(s, 1H), 5.060(s, 1H), 4.15(d, J=8Hz, 1H), 3.62-3.72(m, 1H), 2.75-2.88(m, 4H), 2.34-2.45(m, 1H), 1.87-2.01(m, 2H), 1.72-1.83(m, 1H), 1.43-1.63(m, 4H), 1.38(s, 18H), 1.07-1.31(m, 3H)
IR(cm⁻¹) 3634, 2948, 2864, 1637, 1563, 1434, 1231, 760

35 Example 173

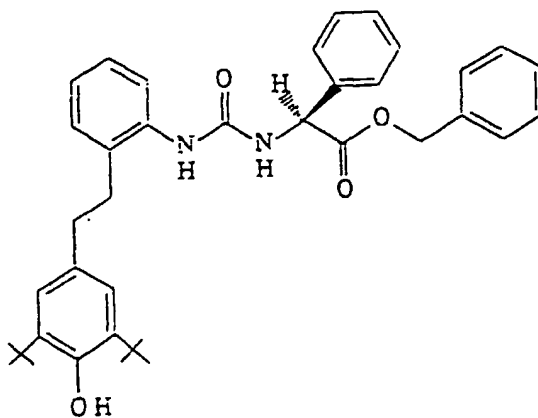
(S)-N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(α-benzyloxycarbonyl)benzylurea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using (S)-α-phenylglycine benzyl ester instead of decylamine.

m.p. 132-134°C

¹H-NMR(δ ppm, CDCl₃) 7.13-7.33(m, 14H), 6.75(s, 2H), 5.57(d, J=8Hz, 1H), 5.27(d, J=7Hz, 1H), 5.15(s, 1H),
5.11(s, 2H), 5.08(s, 1H), 2.74-2.87(m, 4H), 1.34(s, 18H)

5 IR(cm⁻¹) 3642, 3344, 2944, 1749, 1643, 1587, 1553, 1168, 749, 697

Example 174

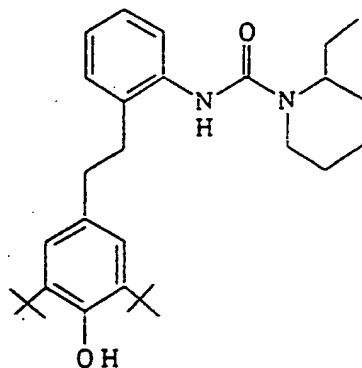
1-[N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]carbamoyl]-2-ethylpiperidine

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 2-ethylpiperidine instead of decylamine. m.p. 137-138°C

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¹H-NMR(δ ppm, CDCl₃) 7.52-7.58(m, 1H), 7.16-7.23(m, 2H), 7.04-7.10(m, 1H), 6.84(s, 2H), 5.78(s, 1H), 5.08(s, 1H), 3.91-4.00(m, 1H), 3.51-3.61(m, 1H), 2.76-2.87(m, 5H), 1.45-1.80(m, 8H), 1.38(s, 18H), 0.86(t, J=7Hz, 3H)
IR(cm⁻¹) 3450, 3300, 2960, 1640, 1510, 1490, 1455, 1250, 885, 765

35 Example 175

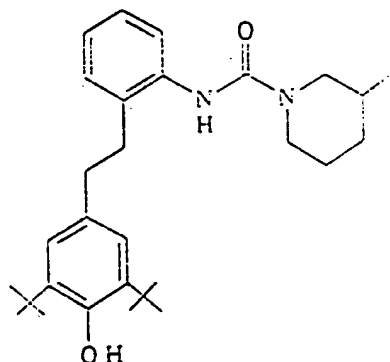
1-[N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]carbamoyl]-3-methylpiperidine

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 3-methylpiperidine instead of decylamine.

EP 0 625 507 B1

¹H-NMR(δ ppm, CDCl₃) 7.49-7.54(m, 1H), 7.16-7.24(m, 2H), 7.07-7.13(m, 1H), 6.83(s, 2H), 5.72(s, 1H), 5.09(s, 1H), 3.80-3.87(m, 1H), 3.46-3.54(m, 1H), 2.82(s, 4H), 2.70-2.82(m, 2H), 2.35-2.44(m, 1H), 1.76-1.84(m, 1H), 1.40-1.67(m, 3H), 1.38(s, 18H), 1.02-1.14(m, 1H), 0.88(t, J=6Hz, 3H)
IR(cm⁻¹) 3645, 3430, 3310, 2960, 2870, 1640, 1525, 1435, 1250, 1150, 750

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Example 176

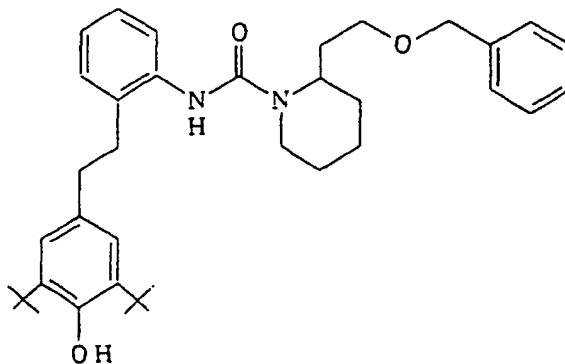
1-[N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]carbamoyl]-2-[2-(benzyloxy)ethyl]piperidine

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 2-[2-(benzyloxy)ethyl]methylpiperidine instead of decylamine.

30 m.p. 113-114°C

¹H-NMR(δ ppm, CDCl₃) 7.53(d, J=8Hz, 1H), 7.02-7.22(m, 8H), 6.89(s, 2H), 6.74(bs, 1H), 5.05(s, 1H), 4.35-4.44(m, 2H), 4.23-4.32(m, 1H), 4.03-4.15(m, 1H), 3.44-3.59(m, 2H), 2.63-2.77(m, 5H), 2.00-2.12(m, 1H), 1.44-1.82(m, 7H), 1.37(s, 18H)

35 IR(cm⁻¹) 3600, 3420, 2940, 2870, 1665, 1595, 1535, 1450, 1400, 1380, 1270, 1240, 1100, 765, 745

Example 177

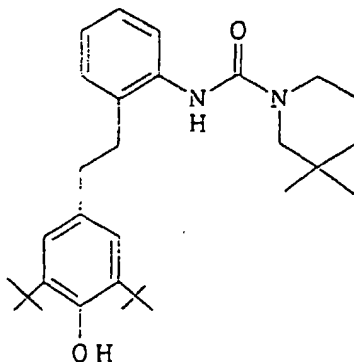
1-[N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]carbamoyl]-3,3-dimethylpiperidine

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 3,3-dimethylpiperidine-

ine instead of decylamine.

¹H-NMR(δ ppm, CDCl₃) 7.54(dd, J=8, 1Hz, 1H), 7.16-7.23(m, 2H), 7.04-7.12(m, 1H), 6.84(s, 2H), 5.77(s, 1H),
5.08(s, 1H), 3.19(t, J=6Hz, 2H), 3.05(s, 2H), 2.82(s, 4H), 1.52-1.61(m, 2H), 1.33-1.43(m, 2H), 1.39(s, 18H), 0.92(s,
5 6H)
IR(cm⁻¹) 3645, 3430, 3320, 2960, 2870, 1640, 1520, 1440, 1250, 1165, 755

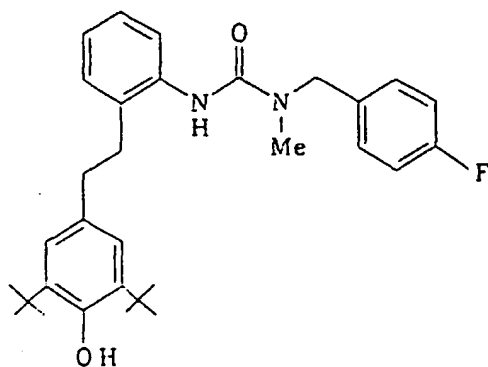
Example 178

10 N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(4-fluorobenzyl)-N'-methylurea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 4-fluoro-N-methyl-phenethylamine instead of decylamine.

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¹H-NMR(δ ppm, CDCl₃) 7.63(d, J=8Hz, 1H), 7.17-7.26(m, 4H), 7.11(dd, J=8, 7Hz, 1H), 6.97(dd, J=9, 9Hz, 2H),
6.75(s, 2H), 5.66(s, 1H), 5.06(s, 1H), 4.45(s, 2H), 2.73-2.84(m, 4H), 2.64(s, 3H), 1.33(s, 18H)
IR(cm⁻¹) 3645, 3430, 3320, 2965, 1650, 1515, 1440, 1380, 1300, 1230, 1160, 760

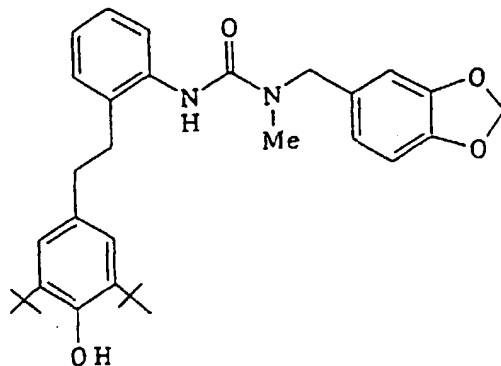
Example 179

40 N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(3,4-methylenedioxybenzyl)-N'-methylurea

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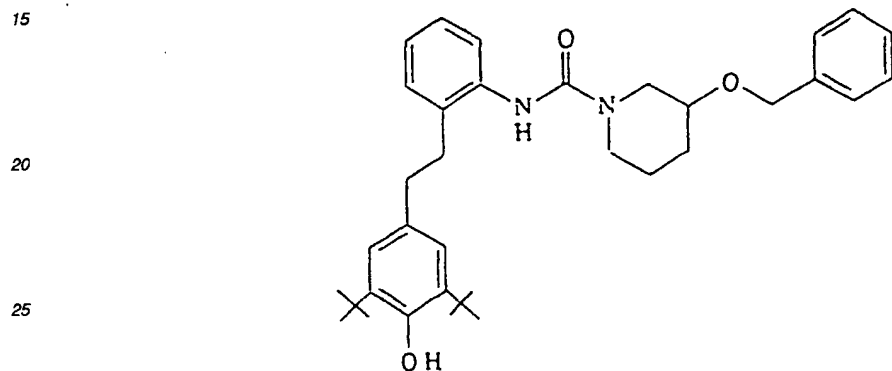
EP 0 625 507 B1

The title compound was prepared in a similar manner to that mentioned in Example 11, using 5-(methylaminomethyl)-1,3-dioxaindane instead of decylamine.
m.p. 152-153°C

5 $^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.65(d, $J=8\text{Hz}$, 1H), 7.16-7.25(m, 2H), 7.10(dd, $J=7$, 7Hz, 1H), 6.76(s, 2H), 6.65-6.73(m, 2H), 5.92(s, 2H), 5.69(s, 1H), 5.06(s, 1H), 4.39(s, 2H), 2.72-2.83(m, 4H), 2.66(s, 3H), 1.34(s, 18H)

Example 180

10 1-[N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]carbamoyl]-3-(benzyloxy)piperidine

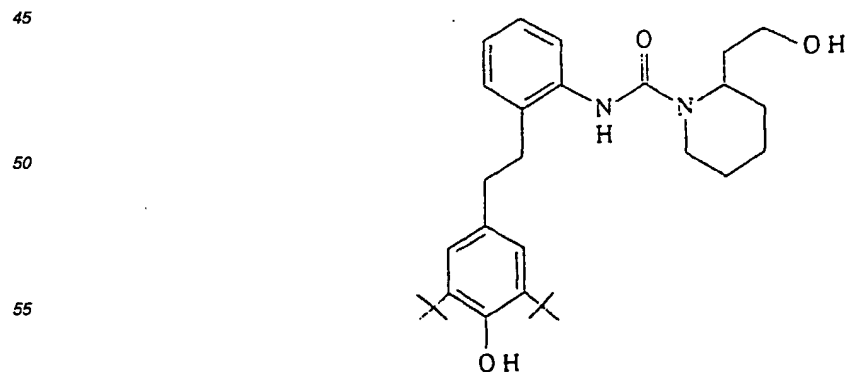


30 The title compound was prepared in a similar manner to that mentioned in Example 11, using 3-benzyloxypiperidine instead of decylamine.

35 $^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.44(d, $J=8\text{Hz}$, 1H), 7.22-7.34(m, 5H), 7.18(dd, $J=7$, 7Hz, 1H), 7.08(dd, $J=7$, 7Hz, 1H), 6.80(s, 2H), 5.82(s, 1H), 5.06(s, 1H), 4.47-4.56(m, 2H), 3.68-3.76(m, 1H), 3.43-3.51(m, 1H), 3.09-3.22(m, 3H), 2.71-2.83(m, 4H), 1.61-1.96(m, 3H), 1.38-1.50(m, 1H), 1.36(s, 18H)
IR(cm^{-1}) 3625, 3280, 2960, 1635, 1525, 1490, 1445, 1245, 1045, 940, 765

Example 181

40 1-[N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]carbamoyl]-2-(2-hydroxyethyl)piperidine



EP 0 625 507 B1

The title compound was prepared in a similar manner to that mentioned in Example 11, using 2-(2-hydroxyethyl)piperidine instead of decylamine.

5 $^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.46(d, $J=8\text{Hz}$, 1H), 7.16-7.24(m, 2H), 7.11(ddd, $J=8, 7, 1\text{Hz}$, 1H), 6.84(s, 2H), 6.00-6.21(br, 1H), 5.08(s, 1H), 4.51-4.62(m, 1H), 3.57-3.66(m, 1H), 3.48-3.18(m, 3H), 2.69-2.88(m, 5H), 1.40-2.03(m, 8H), 1.38(s, 18H)
IR(cm^{-1}) 3640, 3320, 2950, 2870, 1640, 1530, 1440, 1275, 1230, 1175, 755

Example 182

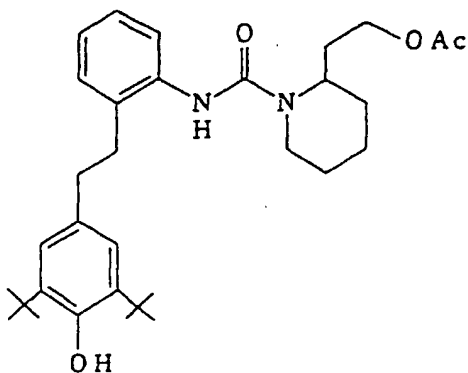
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1-[N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]carbamoyl]-2-(2-acetoxyethyl)piperidine

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 2-(2-acetoxyethyl)piperidine instead of decylamine.

35 $^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.49(d, $J=8\text{Hz}$, 1H), 7.17-7.23(m, 2H), 7.09(d, $J=7\text{Hz}$, 1H), 6.84(s, 2H), 5.84(s, 1H), 5.08(s, 1H), 4.33-4.43(m, 1H), 4.00-4.16(m, 2H), 3.41-3.51(m, 1H), 2.76-2.90(m, 5H), 2.00-2.12(m, 1H), 1.97(s, 3H), 1.74-1.85(m, 1H), 1.38-1.72(m, 6H), 1.38(s, 18H)
IR(cm^{-1}) 3640, 3425, 2960, 2870, 1740, 1640, 1520, 1435, 1370, 1235, 750

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Example 183

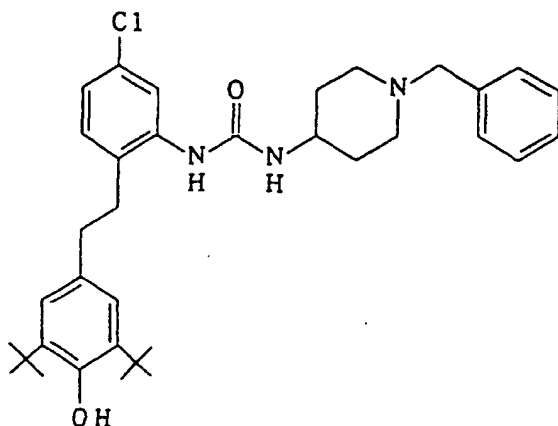
N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)-5-chlorophenyl]N'-(1-benzyl-4-piperidyl)urea

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The title compound was prepared in a similar manner to that mentioned in Example 108, using 4-(2-amino-4-chlorophenethyl)-2,6-di-tert-butylphenol instead of 4-(2-amino-3,5-difluorophenethyl)-2,6-di-tert-butylphenol.

m.p. 155-156°C

$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.41(s, 1H), 7.22-7.31(m, 5H), 7.08(s, 2H), 6.77(s, 2H), 5.22(s, 1H), 5.12(s, 1H), 4.20(d, $J=8\text{Hz}$, 1H), 3.45-3.65(m, 1H), 3.45(s, 2H), 2.75(s, 4H), 2.73-2.77(m, 2H), 2.04(t, $J=11\text{Hz}$, 2H), 1.85(d, $J=11\text{Hz}$, 2H), 1.38(s, 18H), 1.22-1.42(m, 2H)

$\text{IR}(\text{cm}^{-1})$ 3645, 3370, 1633, 1545, 1438, 1234, 699

Example 184

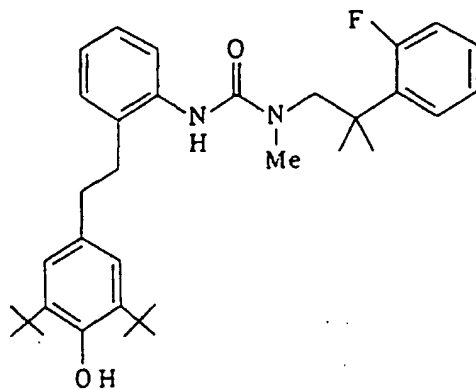
N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)-5-chlorophenyl]-N'-[2-(2-fluorophenyl)-2-methylpropyl]-N'-methylurea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 2-fluoro- β,β -dimethylphenethylamine instead of decylamine.

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$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.53(d, $J=8\text{Hz}$, 1H), 7.17-7.28(m, 4H), 7.05-7.14(m, 2H), 6.94-7.03(m, 1H), 6.73(s, 2H), 5.49(s, 1H), 5.01(s, 1H), 3.70(s, 2H), 2.73-2.83(m, 4H), 2.21(s, 3H), 1.37(s, 6H), 1.29(s, 18H)

$\text{IR}(\text{cm}^{-1})$ 3640, 3430, 2965, 1660, 1510, 1490, 1440, 1210, 760

Example 185

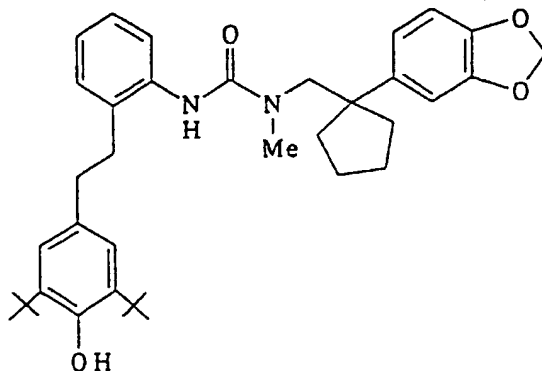
N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)-5-chlorophenyl]-N'-methyl-N'-[1-(3,4-methylenedioxyphenyl)cyclopentyl]methylurea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 5-[1-(N-methylamino)cyclopentyl]-1,3-dioxindane instead of decylamine.

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$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.45(d, $J=7\text{Hz}$, 1H), 7.16-7.24(m, 2H), 7.06-7.13(m, 1H), 6.78(s, 1H), 6.72(s, 4H), 5.92(s, 2H), 5.32(s, 1H), 5.03(s, 1H), 3.42(s, 2H), 2.73-2.82(s, 4H), 2.02(s, 3H), 2.58-2.98(m, 8H), 1.30(s, 18H)
 $\text{IR}(\text{cm}^{-1})$ 3640, 3430, 2960, 1660, 1510, 1490, 1435, 1235, 1450, 760

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Example 186

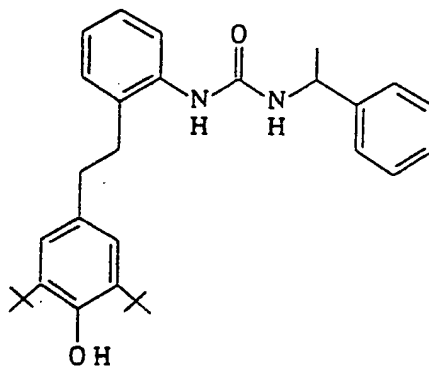
N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)-5-chlorophenyl]-N'-(α -methylbenzyl)urea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using α -methylbenzylamine instead of decylamine. m.p. 167-168°C

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$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.12-7.33(m, 9H), 6.77(s, 2H), 5.15(s, 1H), 5.09(s, 1H), 4.96(dq, $J=7, 7\text{Hz}$, 1H), 4.53(d, $J=7\text{Hz}$, 1H), 2.70-2.82(m, 4H), 1.40(d, $J=7\text{Hz}$, 3H), 1.37(s, 18H)
 $\text{IR}(\text{cm}^{-1})$ 3625, 3320, 3275, 2960, 1630, 1565, 1435, 1235, 745, 700

Example 187

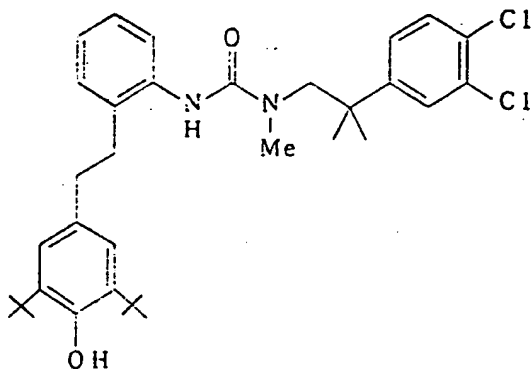
N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)-5-chlorophenyl]-N'-[2-(3,4-dichlorophenyl)-2-methylpropyl]-N'-methylurea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using N-methyl-3,4-dichloro- β,β -dimethylphenethylamine instead of decylamine.

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$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.48(d, $J=8\text{Hz}$, 1H), 7.43(d, $J=2\text{Hz}$, 1H), 7.37(d, $J=10\text{Hz}$, 1H), 7.17-7.27(m, 3H), 7.09-7.15(m, 1H), 6.71(s, 2H), 5.38(s, 1H), 5.08(s, 1H), 3.48(s, 2H), 2.72-2.84(m, 4H), 2.13(s, 3H), 1.36(s, 6H), 1.29(s, 18H)

$\text{IR}(\text{cm}^{-1})$ 3640, 3430, 3330, 2970, 1660, 1515, 1480, 1450, 1440, 1310, 1250, 1030, 880, 760

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Example 188

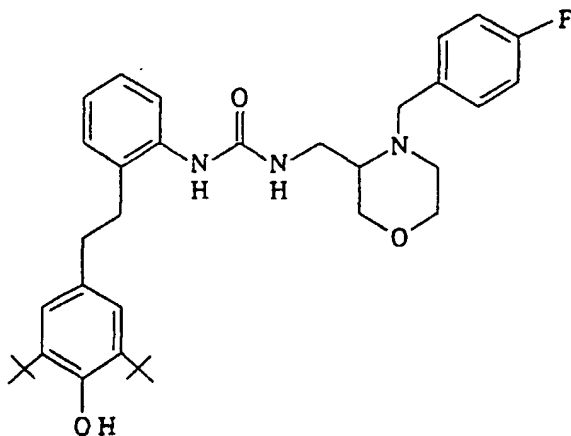
N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)-5-chlorophenyl]-N'-[4-(4-fluorobenzyl)-3-morpholinyl]methylurea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 3-methylamino-4-(4-fluorobenzyl)morpholine instead of decylamine.

$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.19-7.37(m, 4H), 6.80-6.89(m, 4H), 6.76(s, 2H), 5.11(s, 1H), 5.05(s, 1H), 4.96(bs, 1H), 3.89(d, $J=13\text{Hz}$, 1H), 3.74(dd, $J=12, 3\text{Hz}$, 1H), 3.64(d, $J=12\text{Hz}$, 1H), 3.31-3.42(m, 4H), 3.03(d, $J=13\text{Hz}$, 1H), 2.70-

2.88(m, 4H), 2.48-2.56(m, 1H), 2.45(d, J=12Hz, 1H), 2.10(dt, J=11, 3Hz, 1H), 1.37(s, 18H)

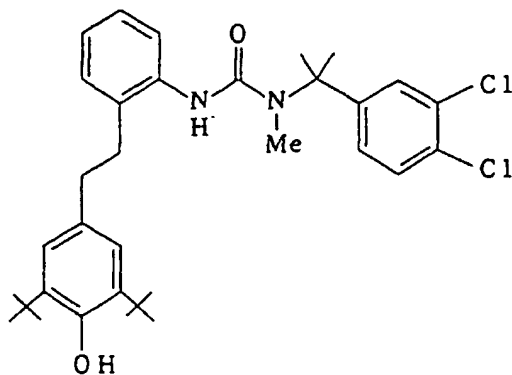
Example 189

5 N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)-5-chlorophenyl]-N'-[2-(3,4-dichlorophenyl)-2-propyl]-N'-methylurea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 3,4-dichloroN, α , α -trimethylbenzylamine instead of decylamine.

30

$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.36-7.42(m, 2H), 7.24-7.29(m, 1H), 7.09-7.17(m, 3H), 7.02-7.07(m, 1H), 6.79(s, 2H), 5.52(s, 1H), 5.09(s, 1H), 2.81(s, 3H), 2.61-2.78(m, 4H), 1.63(s, 6H), 1.38(s, 18H)
 IR(cm^{-1}) 3640, 3290, 2960, 2875, 1640, 1520, 1485, 1440, 1340, 1245, 1140, 1030, 755

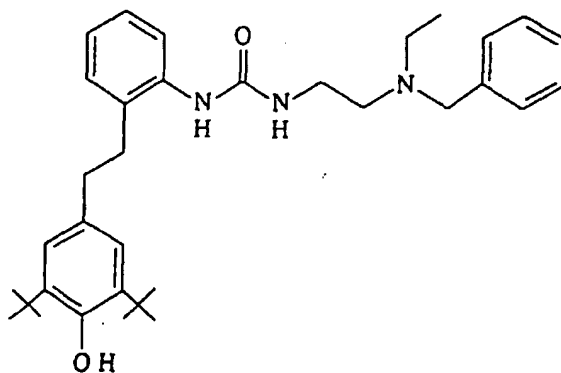
Example 190

35 N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)-5-chlorophenyl]-N'-[2-(N-benzyl-N-ethylamino)ethyl]urea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using N-benzyl-N-ethylethylenediamine instead of decylamine.
 m.p. 132-133°C

EP 0 625 507 B1

$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.16-7.36(m, 7H), 6.92-6.98(m, 2H), 6.79(s, 2H), 5.12(bs, 1H), 5.09(s, 1H), 5.00-5.05(m, 1H), 3.43(s, 2H), 3.21(td, $J=6, 5\text{Hz}$, 2H), 2.74-2.90(m, 4H), 2.46(t, $J=6\text{Hz}$, 2H), 2.37(q, $J=7\text{Hz}$, 2H), 1.38(s, 18H), 0.87(t, $J=7\text{Hz}$, 3H)

$\text{IR}(\text{cm}^{-1})$ 3650, 3340, 3280, 2960, 2810, 1640, 1585, 1560, 1440, 1235, 1150, 865, 745, 705

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Example 191

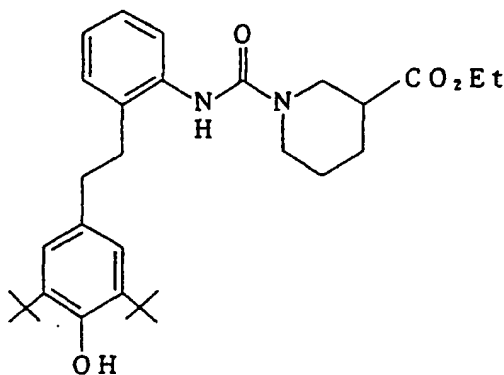
1-[N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]carbamoyl]-3-ethoxycarbonylpiperidine

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25



The title compound was prepared in a similar manner to that mentioned in Example 11, using 3-ethoxycarbonylpiperidine instead of decylamine.

30

$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.53(d, $J=8\text{Hz}$, 1H), 7.15-7.22(m, 2H), 7.04-7.09(m, 1H), 6.84(s, 2H), 6.30(s, 1H), 5.07(s, 1H), 4.06-4.15(m, 2H), 3.74-3.81(m, 1H), 3.30-3.42(m, 2H), 3.10-3.17(m, 1H), 2.78-2.92(m, 4H), 2.52-2.59(m, 1H), 1.83-2.00(m, 2H), 1.46-1.66(m, 2H), 1.38(s, 18H), 1.22(t, $J=7\text{Hz}$, 3H)

$\text{IR}(\text{cm}^{-1})$ 3425, 2945, 2870, 1725, 1650, 1595, 1530, 1450, 1375, 1300, 1210, 1030, 885, 760

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Example 192

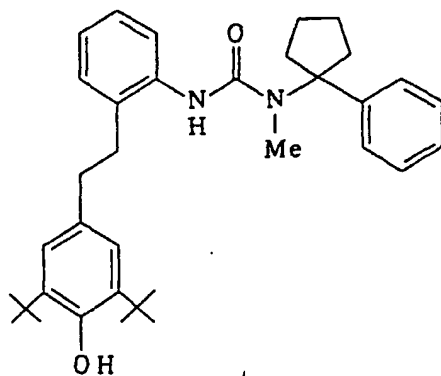
N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)-5-chlorophenyl]-N'-(1-phenylcyclopentyl)-N'-methylurea

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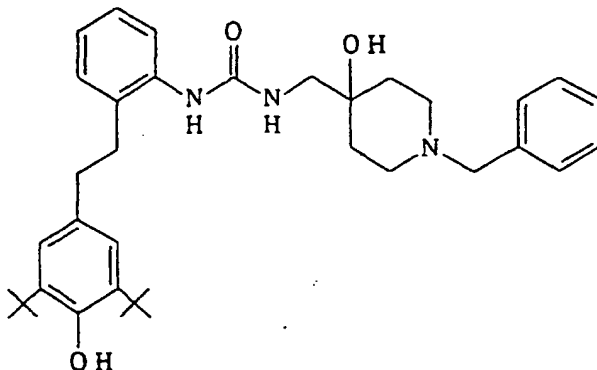
The title compound was prepared in a similar manner to that mentioned in Example 11, using N-methyl-1-phenyl-

cyclopentylamine instead of decylamine.

¹H-NMR(δ ppm, CDCl₃) 7.47(d, J=8Hz, 1H), 7.33(dd, J=8, 1Hz, 1H), 7.08-7.18(m, 3H), 6.93-7.02(m, 3H), 6.78(s, 2H), 5.75(s, 1H), 5.07(s, 1H), 3.15(s, 3H), 2.57(t, J=8Hz, 2H), 2.23-2.39(m, 4H), 2.20(t, J=8Hz, 2H), 1.64-1.85(m, 4H), 1.42(s, 18H)
 IR(cm⁻¹) 3630, 3410, 2950, 1640, 1520, 1440, 1345, 1230, 755, 700

Example 193

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)-5-chlorophenyl]-N'-(1-benzyl-4-hydroxy-4-piperidyl)methylurea

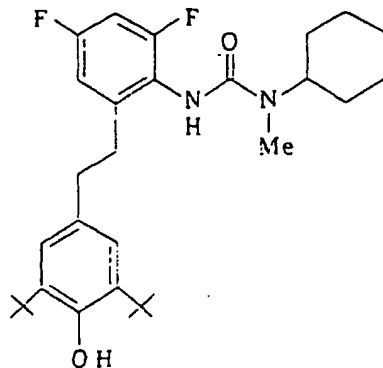


The title compound was prepared in a similar manner to that mentioned in Example 11, using 4-aminomethyl-1-benzyl-4-hydroxypiperidine instead of decylamine.

¹H-NMR(δ ppm, CDCl₃) 7.15-7.35(m, 9H), 6.76(s, 2H), 5.12(s, 1H), 5.08(bs, 1H), 4.56(t, J=5Hz, 1H), 3.51(s, 2H), 3.37(bs, 1H), 3.14(d, J=5Hz, 2H), 2.70-2.85(m, 4H), 2.50-2.60(m, 2H), 2.30-2.40(m, 2H), 1.45-1.60(m, 4H), 1.36(s, 18H)
 IR(cm⁻¹) 3350, 2952, 1639, 1550, 1435, 1234, 741, 699

Example 194

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)-4,6-difluorophenyl]-N'-cyclohexyl-N'-methylurea



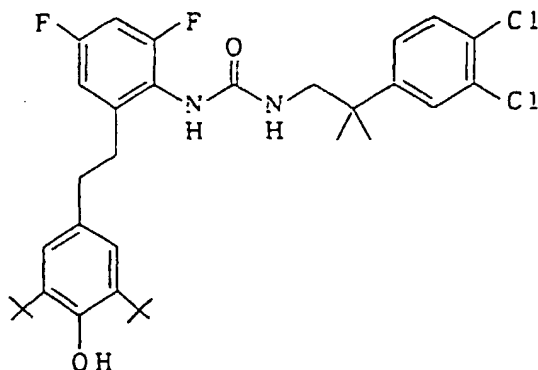
EP 0 625 507 B1

The title compound was prepared in a similar manner to that mentioned in Example 108, using N-methylcyclohexylamine instead of 4-amino-1-benzylpiperidine.

¹H-NMR(δ ppm, CDCl₃) 6.70-6.80(m, 2H), 6.79(s, 2H), 5.09(s, 1H), 4.98(bs, 1H), 4.00-4.10(m, 1H), 2.75-2.90(m, 4H), 2.60(s, 3H), 1.60-1.80(m, 4H), 1.20-1.50(m, 24H)
IR(cm⁻¹) 3630, 3420, 2930, 1639, 1499, 1435, 1317, 1237, 1119

Example 195

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)-4,6-difluorophenyl]-N'-[2-(3,4-dichlorophenyl)-2-methylpropyl]urea

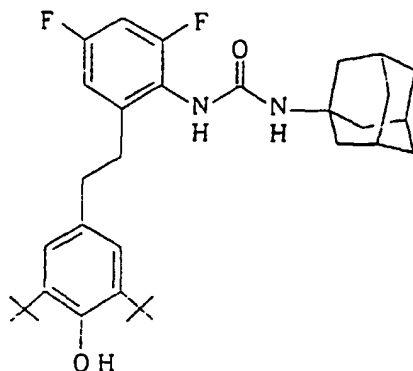


The title compound was prepared in a similar manner to that mentioned in Example 108, using 3,4-dichloro-β,β-dimethylphenethylamine instead of 4-amino-1-benzylpiperidine. m.p. 159-160°C

¹H-NMR(δ ppm, CDCl₃) 7.05-7.30(m, 3H), 6.65-6.78(m, 4H), 5.08-5.11(m, 1H), 4.27(bs, 1H), 3.72(bt, J=6Hz, 1H), 3.28-3.31(m, 2H), 2.65-2.80(m, 4H), 1.30-1.40(m, 18H), 1.20-1.30(m, 6H)
IR(cm⁻¹) 3640, 3310, 2958, 1638, 1566, 1436, 1235, 1118

Example 196

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)-4,6-difluorophenyl]-N'-(1-adamantyl)urea



EP 0 625 507 B1

The title compound was prepared in a similar manner to that mentioned in Example 108, using 1-adamantanamine instead of 4-amino-1-benzylpiperidine.

m.p. 218-220°C

5 $^1\text{H-NMR}$ (δ ppm, CDCl_3) 6.81(s, 2H), 6.70-6.80(m, 2H), 5.12(s, 1H), 4.60(bs, 1H), 3.93(bs, 1H), 2.88(t, $J=7\text{Hz}$, 2H), 2.78(t, $J=7\text{Hz}$, 2H), 2.03(bs, 3H), 1.91(d, $J=3\text{Hz}$, 6H), 1.64(bs, 6H), 1.40(s, 18H)
IR(cm^{-1}) 3642, 3375, 2910, 1650, 1562, 1495, 1436, 1235, 1120

Example 197

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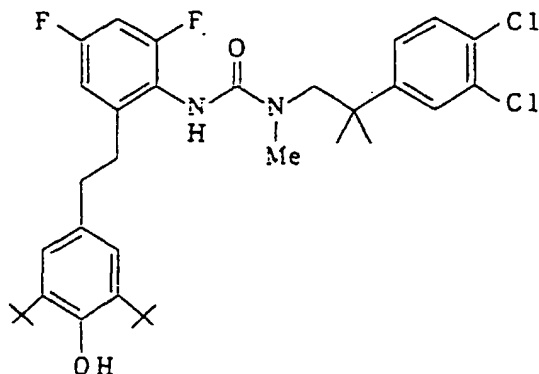
N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)-4,6-difluorophenyl]-N'-[2-(3,4-dichlorophenyl)-2-methylpropyl]-N'-methylurea

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The title compound was prepared in a similar manner to that mentioned in Example 108, using N-methyl-3,4-dichloro- β,β -dimethylphenethylamine instead of 4-amino-1-benzylpiperidine. m.p. 145-147°C

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$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.15-7.40(m, 3H), 6.65-6.80(m, 4H), 5.04-5.06(m, 1H), 4.70-4.73(m, 1H), 3.46-3.49(m, 2H), 2.75-2.85(m, 4H), 2.20-2.24(m, 3H), 1.30-1.34(m, 24H)
IR(cm^{-1}) 3572, 3420, 2954, 1665, 1505, 1434, 1120

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Example 198

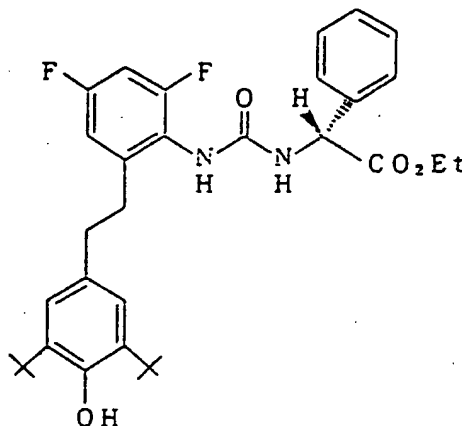
(R)-N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)-4,6-difluorophenyl]-N'-(α -ethoxycarbonylbenzyl)urea

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The title compound was prepared in a similar manner to that mentioned in Example 108, using (R)- α -phenylglycine ethyl ester instead of 4-amino-1-benzylpiperidine. m.p. 162-164°C

$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.26-7.32(m, 5H), 6.73-6.80(m, 4H), 5.45(d, J=7Hz, 1H), 5.22(bd, J=7Hz, 1H), 5.12(s, 1H), 4.68(bs, 1H), 4.08-4.20(m, 2H), 2.72-2.89(m, 4H), 1.37(s, 18H), 1.18(t, J=7Hz, 3H)
 $\text{IR}(\text{cm}^{-1})$ 3640, 3350, 2956, 1737, 1641, 1561, 1438, 1122

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Example 199

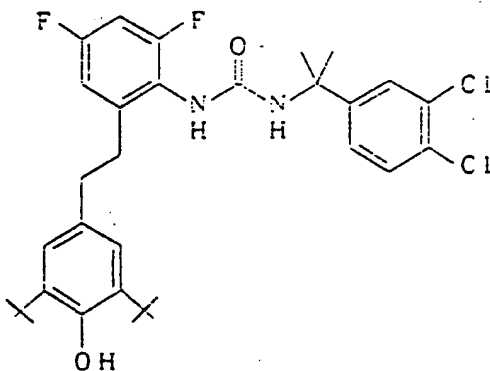
N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)-4,6-difluorophenyl]-N'-[2-(3,4-dichlorophenyl)-2-propyl]urea

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The title compound was prepared in a similar manner to that mentioned in Example 108, using 3,4-dichloro- α,α -dimethylbenzylamine instead of 4-amino-1-benzylpiperidine. m.p. 224-226°C

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$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.42(d, J=2Hz, 1H), 7.31(d, J=9Hz, 1H), 7.18(dd, J=9, 2Hz, 1H), 6.75-6.80(m, 4H), 5.13(s, 1H), 4.62(bs, 1H), 4.53(bs, 1H), 2.56(t, J=7Hz, 2H), 2.77(t, J=7Hz, 2H), 1.57(s, 6H), 1.40(s, 18H)
 $\text{IR}(\text{cm}^{-1})$ 3634, 3354, 2954, 1649, 1562, 1435, 1277, 1238, 1122

Example 200

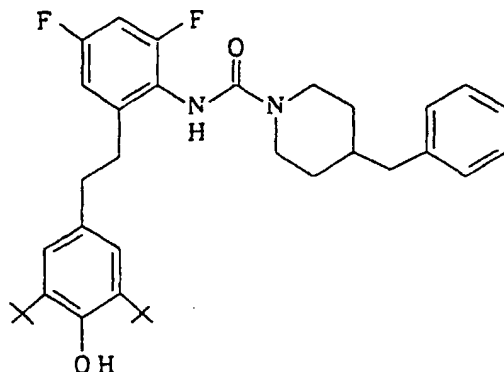
1-[N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)-4,6-difluorophenyl]carbamoyl]-4-benzylpiperidine

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The title compound was prepared in a similar manner to that mentioned in Example 108, using 4-benzylpiperidine instead of 4-amino-1-benzylpiperidine.

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$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.25-7.31(m, 2H), 7.20(t, $J=7\text{Hz}$, 1H), 7.12(d, $J=7\text{Hz}$, 2H), 6.71-6.80(m, 2H), 6.75(s, 2H), 5.09(s, 1H), 4.96(s, 1H), 3.73(bd, $J=13\text{Hz}$, 2H), 2.78-2.85(m, 4H), 2.67(t, $J=12\text{Hz}$, 2H), 2.53(d, $J=7\text{Hz}$, 2H), 1.58-1.71(m, 3H), 1.36(s, 18H), 1.12-1.22(m, 2H)

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$\text{IR}(\text{cm}^{-1})$ 3636, 3418, 3026, 1627, 1499, 1435, 1235, 1120, 789, 748, 700

Example 201

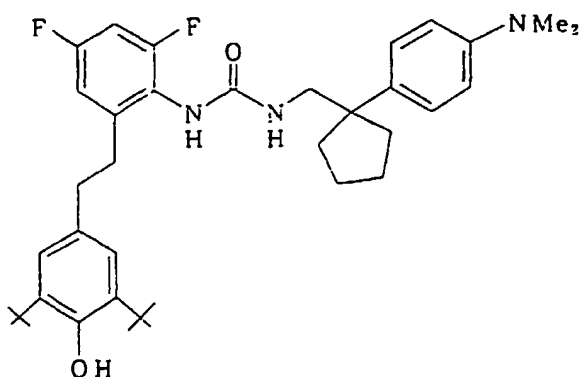
N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)-4,6-difluorophenyl]-N'-[1-(4-dimethylaminophenyl)cyclopentyl]methylurea

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The title compound was prepared in a similar manner to that mentioned in Example 108, using 4-[(1-aminomethyl)-1-cyclopentyl]-N,N-dimethylaniline instead of 4-amino-1-benzylpiperidine. m.p. 165-166°C

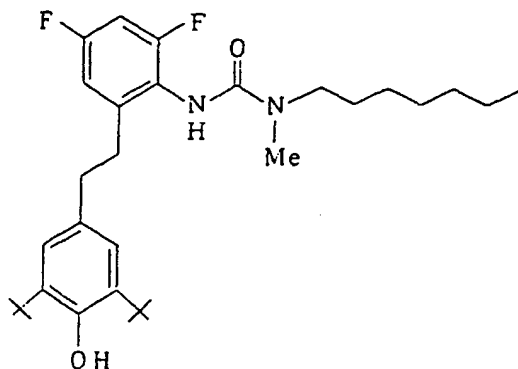
55

$^1\text{H-NMR}$ (δ ppm, CDCl_3) 6.92(d, $J=9\text{Hz}$, 2H), 6.75(s, 2H), 6.68-6.76(m, 2H), 6.54(d, $J=9\text{Hz}$, 2H), 5.08(s, 1H), 4.59(s, 1H), 3.82(bs, 1H), 3.19(d, $J=6\text{Hz}$, 2H), 2.89(s, 6H), 2.76(t, $J=7\text{Hz}$, 2H), 2.67(t, $J=7\text{Hz}$, 2H), 1.67-1.90(m, 8H), 1.37(s, 18H)

IR(cm^{-1}) 3674, 3250, 1615, 1520, 1435, 1233, 1121

Example 202

5 N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)-4,6-difluorophenyl]-N'-heptyl-N'-methylurea



25 The title compound was prepared in a similar manner to that mentioned in Example 108, using N-methylheptylamine instead of 4-amino-1-benzylpiperidine.

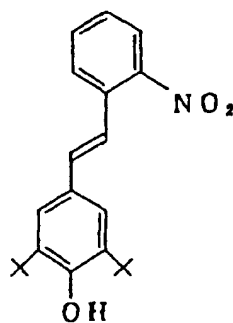
30 $^1\text{H-NMR}$ (δ ppm, CDCl_3) 6.70-6.80(m, 2H), 6.77(s, 2H), 5.10(s, 1H), 4.96(s, 1H), 3.21(t, $J=8\text{Hz}$, 2H), 2.75-2.86(m, 4H), 2.75(s, 3H), 1.42-1.56(m, 2H), 1.37(s, 18H), 1.20-1.35(m, 8H), 0.87(t, $J=7\text{Hz}$, 3H)
IR(cm^{-1}) 3640, 3300, 1638, 1503, 1435, 1236, 1120

The preparation of the compound of formula (II) used in each of the above examples is illustrated by the following reference examples.

35 Reference Example 1

4-(2-Aminophenethyl)-2,6-di-tert-butylphenol

40 (1) 2,6-di-tert-Butyl-4-(2-nitrostyryl)phenol



To a solution of 3,5-di-tert-butyl-4-hydroxybenzaldehyde (8.09 g, 34.5 mmol) and 2-nitrophenylacetic acid (9.40 g,

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51.9 mmol) in xylene (60 ml) was added piperidine (0.3 ml) and the mixture was heated under reflux for 26 hrs while removing water producing with the progress of reaction. After allowing to stand overnight, hexane was added to afford as crystals 2,6-di-tert-butyl-4-(2-nitrostyryl)phenol (7.67 g, 62.9%).

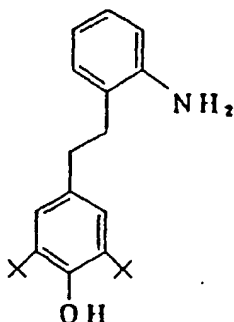
5 $^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.94(dd, $J=8$, 1Hz, 1H), 7.76(d, $J=8\text{Hz}$, 1H), 7.57(dd, $J=8$, 8Hz, 1H), 7.44(d, $J=16\text{Hz}$, 1H), 7.33-7.37(m, 3H), 7.07(d, $J=16\text{Hz}$, 1H), 5.38(s, 1H), 1.48(s, 18H)

(2) 4-(2-Aminophenethyl)-2,6-di-tert-butylphenol

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To a suspension of 2,6-di-tert-butyl-4-(2-nitrostyryl)phenol (16.4 g, 23.3 mmol) in ethanol (150 ml) was added a catalytic amount of 10% palladium carbon and the suspension was subjected to catalytic reduction at room temperature at 1-2.5 atms for 8 hrs and at 40°C for 3 hrs. After filtering the catalyst, distilling off the solvent gave 4-(2-aminophenethyl)-2,6-di-tert-butylphenol (15.1 g, 100%) as a viscous oil.

30

$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.02-7.07(m, 2H), 6.94(s, 2H), 6.74-6.78(m, 1H), 6.67(d, $J=8\text{Hz}$, 1H), 5.06(s, 1H), 3.3-3.7(bs, 2H), 2.73-2.87(m, 4H), 1.41(s, 18H)

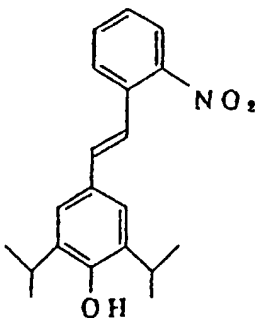
35 Reference Example 2

(1) 2,6-Diisopropyl-4-(2-nitrostyryl)phenol

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55 To a solution of 3,5-diisopropyl-4-hydroxybenzaldehyde (0.95 g, 4.6 mmol) and 2-nitrophenyl acetic acid (1.1 g, 6.2 mmol) in xylene (10 ml) was added piperidine (0.05 ml) and the mixture was heated under reflux for 8 hrs while removing water producing with the progress of reaction. After distilling off the solvent followed by purification of the residue by a silica gel column chromatography, recrystallization from hexane gave 2,6-diisopropyl-4-(2-nitrostyryl)phenol (1.3 g, 87%) as crystals.

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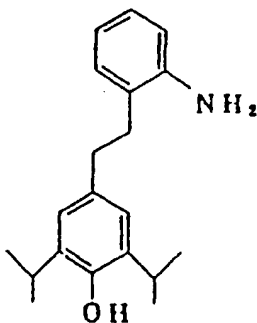
¹H-NMR (δ ppm, CDCl₃) 7.93-7.95(m, 1H), 7.75-7.77(m, 1H), 7.55-7.57(m, 1H), 7.45(d, J=16Hz, 1H), 7.34-7.38(m, 1H), 7.24(s, 2H), 7.07(d, J=16Hz, 1H), 4.95(s, 1H), 3.12-3.22(m, 2H), 1.32(s, 6H), 1.30(s, 6H)

(2) 4-(2-Aminophenethyl)-2,6-diisopropylphenol

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To a suspension of 2,6-diisopropyl-4-(2-nitrostyryl)phenol (1.3 g, 4.0 mmol) in ethanol (20 ml) was added a catalytic amount of 10% palladium carbon and the suspension was subjected to catalytic reduction at 1-2.5 atms at room temperature for 7 hrs. After filtering the catalyst, distilling off the solvent gave 4-(2-aminophenethyl)-2,6-diisopropylphenol (1.0 g, 84%) as a viscous oil.

25

¹H-NMR (δ ppm, CDCl₃) 7.02-7.06(m, 2H), 6.83(s, 2H), 6.70-6.77(m, 1H), 6.65(d, J=7Hz, 1H), 4.67(s, 1H), 3.43(bs, 2H), 3.08-3.18(m, 2H), 2.73-2.87(m, 4H), 1.24(s, 6H), 1.22(s, 6H)

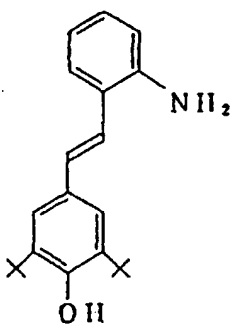
30 Reference Example 3

4-(2-Aminostyryl)-2,6-di-tert-butylphenol

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To a solution of 2,6-di-tert-butyl-4-(2-nitrostyryl)phenol (1.1 g, 3.1 mmol) in methanol (15 ml) was added water (4 ml), conc. hydrochloric acid (0.2 ml) and iron powder (1.7 g, 30 mmol) and the mixture was heated under reflux for 5 hrs. After filtration, followed by extraction with ethyl acetate and water, the extract was washed with water, dried over MgSO₄ and concentrated. Purification of the residue by a silica gel column chromatography followed by recrystallization from hexane afforded 4-(2-aminostyryl)-2,6-di-tert-butylphenol (0.70 g, 70%).

55

¹H-NMR (δ ppm, CDCl₃) 7.36-7.38(m, 1H), 7.34(s, 2H), 7.06-7.10(m, 1H), 6.91-7.10(m, 2H), 6.78-6.82(m, 1H), 6.70-6.72(m, 1H), 5.29(s, 1H), 3.79(s, 2H), 1.47(s, 18H)

Pharmacological Test

1. ACAT inhibitory activity

5 The enzyme preparation, ACAT was prepared from liver microsme fractions of male rabbits according to the method of E. E. Largis et al. (Journal of Lipid Research, Vol. 30, pages 681-690, 1989). The activity was calculated by assaying the amount of the labelled cholesteryl esters formed from [1-¹⁴C]oleoyl-CoA and endogenous cholesterol according to the method of Kazuichi NATORI et al. (Japan J. Pharmacol., Vol. 42, pages 517-523, 1986).

10 The result is shown in Table 1, in which percent inhibition of the formation of the labelled cholesteryl esters with a compound added at 10⁻⁷M is indicated as index for the ACAT inhibitory activity.

The data reveals that the compounds of the invention have a superior ACAT inhibitory activity.

2. Antioxidative activity

15 Human LDL was incubated in the presence of cupric sulfate (5 x 10⁻⁶M) and in the presence or absence of a compound (10⁻⁵M) for 5 hrs. After the incubation, the peroxidation of low-density lipoproteins (LDL) is evaluated by the formation of malondialdehyde (MDA), which is a sort of lipid peroxides according to the method of Simon J. T. Mao et al. (J. Med. Chem., Vol. 34, pages 298-302, 1991). Activity of the compound is shown by percent inhibition of the MDA formation as compared with control. The result is shown in Table 1. The data indicates that the compounds of the invention significantly lower the formation of the lipid peroxide (MDA). 3. Cholesterol-lowering activity

20 Sprague-Dawley male rats were given a powdery feed containing 1% cholesterol and 0.5% cholic acid in an amount of 15 g per day per animal for 3 days to produce hypercholesteremic rats. Four days later, a compound suspended in 0.5% methylcellulose was administered orally at a dose of 30 mg/kg. Blood was drawn prior to and 5 hrs after the administration of the compound, for which the plasma cholesterol level was measured using a commercially available assay kit (Cholesterol E Test Wako, Wako Junyaku K.K.). The result is shown in Table 2.

25 The data shows that the compounds of the invention significantly reduce blood cholesterol level.

Table 1

30	<u>Compounds of Example</u>	<u>ACAT Inhibition (%)</u>	<u>Antioxidant Activity (%)</u>
	1	83	94
35	4	95	98
	5	89	100
40	6	99	98
	12	91	94
	13	90	92
45	14	93	98
	15	76	99
50	16	93	95
	17	92	99
	18	97	97

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	19	100	94
5	29	99	95
	30	84	92
	35	82	94
10	38	71	94
	39	88	87
15	40	96	98
	41	97	99
	42	95	97
20	43	99	99
	44	90	94
25	50	88	90
	52	97	94
	57	89	95
30	69	96	95
	72	97	97
35	74	96	95
	75	88	95
	76	98	96
40	77	96	95
	80	92	96
45	83	96	96
	85	97	94
	90	92	93
50	92	99	96
	97	89	96

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	99	100	95
5	108	97	93
	114	82	98
	115	87	98
10	117	91	97
	124	81	95
15	130	99	95
	140	96	
	141	86	
20	146	85	
	155	94	
25	159	97	
	163	81	
	165	99	
30	166	100	
	167	100	
35	168	93	
	173	95	
40	177	98	
	183	91	

Table 2

Compound of Example	Percent Reduction of Cholesterol (%)
35	48.4
83	44.6
92	79.9
105	45.9
108	71.8
130	71.5

The pharmaceutical preparations comprising the compounds of the invention are prepared by conventional method in accordance with the following formulations.

5

Tablets (per tablet)	
Compound of Example 6	50 mg
Hydroxypropylcellulose	2 mg
Corn starch	10 mg
Lactose	100 mg
Magnesium stearate	3 mg
Talc	3 mg

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Capsules (per capsule)	
Compound of Example 17	200 mg
Starch	8 mg
Microcrystalline cellulose	23 mg
Talc	8 mg
Magnesium stearate	5 mg

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Granules (per divided packet)	
Compound of Example 41	1 mg
Lactose	99 mg
Corn starch	50 mg
Crystalline cellulose	50 mg
Hydroxypropylcellulose	10 mg
Ethanol	9 mg

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Claims

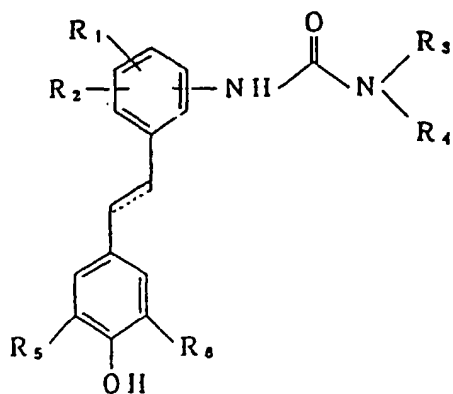
50 1. A compound of formula (I) or a pharmaceutically acceptable salt thereof

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(I)

in which:

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R₁ and R₂, which may be the same or different, each represents

25

- a hydrogen atom,
- a halogen atom,
- a straight or branched (C₁-C₆)alkyl group or
- a straight or branched (C₁-C₆)alkoxy group,

R₃ and R₄, which may be the same or different, each represents

30

- a hydrogen atom,
- a straight or branched (C₁-C₁₂)alkyl group,
- a straight or branched (C₂-C₂₀)alkenyl group,
- a (C₁-C₆)alkoxy(C₁-C₆)alkyl group,
- a (C₁-C₆)alkoxycarbonyl(C₁-C₉)alkyl group,
- a benzyloxycarbonyl(C₁-C₆)alkyl group in which the alkyl moiety is optionally substituted by phenyl,
- a N,N-di(C₁-C₆)alkylamino(C₁-C₆)alkyl group,
- a N-(C₁-C₆)alkyl-N-benzylamino(C₁-C₆)alkyl group,
- a (C₁-C₆)alkylthio(C₁-C₆)alkyl group,
- an oxo(C₁-C₉)alkyl group,
- a hydroxy(C₁-C₆)alkyl group,
- a dihydroxy(C₁-C₆)alkyl group,
- a cyclo(C₃-C₁₅)alkyl group,
- a cyclo(C₃-C₈)alkyl(C₁-C₆)alkyl group,
- a dicyclo(C₃-C₉)alkyl(C₁-C₆)alkyl group,
- a bicyclo(C₆-C₉)alkyl group,

55

a tricyclo(C₉-C₁₂)alkyl group,

in which in all cases the cycloalkyl group or the cycloalkyl moiety is optionally substituted by one or two substituents selected from the group consisting of (C₁-C₆)alkyl, hydroxy, amino, acetoxy, acetamido, phenyl, benzyloxy, dimethylaminophenyl, and methylenedioxyphenyl, which may be further fused with a benzene ring,

an aryl group,

an aryl(C₁-C₆)alkyl group,

a diaryl(C₁-C₆)alkyl group,

in which in all cases the aryl group or the aryl moiety is optionally substituted by one, two or three substituents selected from the group consisting of (C₁-C₆)alkyl, (C₁-C₆)alkyloxy, halogen, nitro, hydroxy, amino, dimethylamino, methylenedioxy, and pyrrolidinyl,

a heterocyclic group or

a heterocyclic group attached to a (C₁-C₆)alkylene chain,

in which in all cases the heterocyclic group represents a saturated or unsaturated, 5 to 8 membered ring monocyclic or bicyclic, heterocyclic group containing 1 to 3 heteroatoms selected from the group consisting of S, O and N, and the heterocyclic group is optionally substituted by one or two substituents selected from the group consisting of acetyl, hydroxy, (C₁-C₉)alkyl, (C₁-C₉)alkyloxy, cyclo(C₃-C₈)alkyl, cyclo(C₃-C₈)alkyl(C₃-C₁₀)alkyl, pyridyl(C₁-C₆)alkyl, phenyl, phenyl(C₁-C₆)alkyl, diphenyl(C₁-C₆)alkyl, and phenylpiperazinyl, the phenyl group or the phenyl moiety being optionally substituted by one or two substituents selected from the group consisting of halogen, hydroxy, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, cyano, diethylamino and trifluoromethyl, which may be further fused with a benzene ring,

and further R₃ and R₄, together with the nitrogen atom to which they are attached, may form a saturated or unsaturated heterocyclic group,

in which the heterocyclic group represents a 5 to 8 membered ring monocyclic or bicyclic, heterocyclic group or a group derived from a heterocyclic spiro compound, which may contain one or two heteroatoms selected from the group consisting of S, O or N, the heterocyclic group being optionally substituted by one or two substituents selected from the group consisting of (C₁-C₆)alkyl, hydroxy, hydroxy(C₁-C₆)alkyl, (C₁-C₆)alkoxy(C₁-C₆)alkyl, acetoxy(C₁-C₆)alkyl, (C₁-C₉)alkylcarbonyl, (C₁-C₆)alkoxycarbonyl, amino, tosyl, phenyl, halogenophenyl, (C₁-C₆)alkoxyphenyl, phenyl(C₁-C₆)alkyl, benzyloxy, benzyloxy(C₁-C₆)alkyl, tolyl, xylyl, benzoyl, methylenedioxyphenyl(C₁-C₆)alkyl, pyridyl, pyridylcarbonyl, piperidyl, pyrrolidinyl(C₁-C₆)alkyl and pyrrolidinylcarbonyl(C₁-C₆)alkyl, which may be further fused with a benzene ring,

in which in all cases the alkyl and alkoxy moieties may be either straight or branched,

with the proviso that both R₃ and R₄ do not represent a hydrogen atom at the same time;

R₅ and R₆, which may be the same or different, each represents a straight or branched (C₁-C₆)alkyl group; and the line



represents -CH₂CH₂- or -CH=CH-.

2. A compound of claim 1 wherein R₃ and R₄, which may be the same or different, each represents

a hydrogen atom,

a straight or branched (C₁-C₁₀)alkyl group,

a straight or branched (C₃-C₁₇)alkenyl group,

a (C₁-C₄)alkoxy(C₁-C₄)alkyl group,

a (C₁-C₄)alkoxycarbonyl(C₁-C₄)alkyl group,

a benzyloxy carbonyl(C₁-C₄)alkyl group in which the alkyl moiety is optionally substituted by phenyl,

a (C₁-C₄)alkylthio(C₁-C₄)alkyl group, a cyclo(C₃-C₁₂)alkyl group or a cyclo(C₅-C₇)alkyl(C₁-C₄)alkyl group in which the cycloalkyl group or the cycloalkyl moiety is optionally monosubstituted by a substituent selected from the group consisting of (C₁-C₄)alkyl, hydroxy, amino, acetoxy, acetamide, phenyl, benzyloxy, dimethylaminophenyl and methylenedioxyphenyl, or the cycloalkyl group or the cycloalkyl moiety is optionally fused with a benzene ring;

a dicyclohexyl(C₁-C₄)alkyl group, a bicyclooctyl group, an adamantyl group, a phenyl group optionally substituted by (C₁-C₄)alkyl or hexyloxy, a naphthyl group, an anthryl group,

a phenyl(C₁-C₄)alkyl group in which the phenyl moiety is optionally substituted by one or two substituents selected from the group consisting of (C₁-C₄)alkyl, (C₁-C₄)alkyloxy, halogen, nitro, hydroxy, amino, dimethylamino, methylenedioxy and pyrrolidinyl;

a diphenyl(C₁-C₄)alkyl group, a heterocyclic group or a heterocyclic group attached to a (C₁-C₄)alkylene chain in which the heterocyclic group represents a saturated or unsaturated, 5 or 6 membered ring monocyclic or bicyclic, heterocyclic group containing 1 or 2 nitrogen atoms and the heterocyclic group is optionally substituted by one or two substituents selected from the group consisting of acetyl, hydroxy, (C₁-C₆)alkyl, cyclohexyl, pyridyl(C₁-C₄)alkyl, phenyl(C₁-C₄)alkyl or diphenyl(C₁-C₄)alkyl in which the phenyl moiety is optionally substituted by one or two substituents selected from the group consisting of halogen, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, cyano, diethylamino and trifluoromethyl, and phenylpiperazinyl, which may be further fused with a benzene ring;

and further R₃ and R₄, together with the nitrogen atom to which they are attached may form a saturated or unsaturated heterocyclic ring, in which the heterocyclic group represents a 5 to 7 membered ring monocyclic or bicyclic, heterocyclic group or a group derived from a heterocyclic spiro compound, which contain one or two nitrogen atoms, the heterocyclic group being optionally substituted by one or two substituents selected from the group consisting of (C₁-C₄)alkyl, hydroxy(C₁-C₄)alkyl, acetoxy(C₁-C₄)alkyl, (C₁-C₆)alkylcarbonyl, (C₁-C₄)alkoxycarbonyl, tosyl, phenyl, phenyl(C₁-C₄)alkyl, benzyloxy, benzyloxy(C₁-C₄)alkyl, benzoyl, methylenedioxyphenyl(C₁-C₄)alkyl, pyridylcarbonyl, piperidyl and pyrrolidinylcarbonyl(C₁-C₄)alkyl.

3. A compound of claim 2 wherein R₃ and R₄, which may be the same or different, each represents a hydrogen atom, a straight or branched (C₁-C₇)alkyl group, a cyclo(C₄-C₈)alkyl group, a heterocyclic group or a heterocyclic group attached to a (C₁-C₄)alkylene chain in which the heterocyclic group represents a saturated or unsaturated, 5 or 6 membered ring monocyclic or bicyclic, heterocyclic group containing one nitrogen atom and the heterocyclic group is optionally substituted by one or two substituents selected from the group consisting of methyl, ethyl, cyclohexyl, pyridylmethyl, and phenyl(C₁-C₃)alkyl in which the phenyl moiety being optionally substituted by one or two substituents selected from the group consisting of halogen, methoxy, cyano, dimethylamino and trifluoromethyl, which may be further fused with a benzene ring.

4. A compound of claim 3 wherein R₃ and R₄, which may be the same or different, each represents a hydrogen atom, a straight or branched (C₁-C₄)alkyl group, cyclohexyl, cycloheptyl, pyrrolidinyl or piperidyl, the latter two heterocyclic groups being optionally substituted by one or two substituents selected from the group consisting of methyl, ethyl, cyclohexyl, pyridylmethyl, and phenyl(C₁-C₃)alkyl in which the phenyl moiety being optionally substituted by one or two substituents selected from the group consisting of halogen, methoxy, cyano, diethylamino and trifluoromethyl, which may be further fused with a benzene ring.

5. A compound of claim 2 wherein R₃ and R₄, together with the nitrogen atom to which they are attached, may form a saturated or unsaturated heterocyclic ring, in which the heterocyclic group represents a 5 or 6 membered ring monocyclic or bicyclic, heterocyclic group which contain one or two nitrogen atoms, the heterocyclic group being optionally substituted by one or two substituents selected from the group consisting of methyl, hydroxyethyl, acetoxyethyl, pentylcarbonyl, ethoxycarbonyl, tosyl, phenyl, benzyl, benzyloxy, benzyloxyethyl, benzoyl, methylenedioxybenzyl, pyridylcarbonyl and piperidyl, which may be further fused with a benzene ring.

6. A compound of formula (I) or a pharmaceutically acceptable salt thereof as claimed in any of claims 1 to 5 for use in therapy.

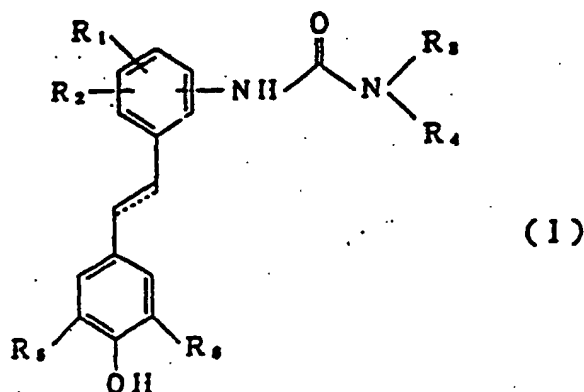
7. A compound as claimed in claim 6 for use in ACAT inhibition.

8. A pharmaceutical composition comprising as an active ingredient a compound of formula (I) or a pharmaceutically acceptable salt thereof as claimed in any of claims 1 to 5 and a pharmaceutically acceptable carrier and/or excipient.

9. Use of a compound of formula (I) or a pharmaceutically acceptable salt thereof as claimed in any of claims 1 to 5 in the manufacture of a medicament for the prophylaxis and treatment of hypercholesterolemia and atherosclerosis.

Patentansprüche

1. Verbindung der Formel (I) oder ein pharmazeutisch verträgliches Salz davon



worin:

R_1 und R_2 , die gleich oder verschieden sein können, jeweils ein Wasserstoffatom,

ein Halogenatom,

eine gerade oder verzweigte (C_1 - C_6) Alkylgruppe oder

eine gerade oder verzweigte (C_1 - C_6) Alkoxygruppe wiedergeben,

R_3 und R_4 , die gleich oder verschieden sein können, jeweils ein Wasserstoffatom,

eine gerade oder verzweigte (C_1 - C_{12}) Alkylgruppe,

eine gerade oder verzweigte (C_2 - C_{20}) Alkenylgruppe,

eine (C_1 - C_6) Alkoxy(C_1 - C_6) alkylgruppe,

eine (C_1 - C_6) Alkoxy-carbonyl(C_1 - C_6) alkylgruppe,

eine Benzoyloxy-carbonyl(C_1 - C_6) alkylgruppe, bei der die Alkylfunktionalität optional durch Phenyl substituiert ist,

eine N,N-di-(C_1 - C_6) Alkylamino(C_1 - C_6) alkylgruppe,

eine N-(C_1 - C_6) Alkyl-N-benzylamino(C_1 - C_6) alkylgruppe,

eine (C_1 - C_6) Alkylthio(C_1 - C_6) alkylgruppe,

eine Oxo(C_1 - C_9) alkylgruppe,

eine Hydroxy(C_1 - C_6) alkylgruppe,

eine Dihydroxy(C_1 - C_6) alkylgruppe,

eine Cyclo(C_3 - C_{15}) alkylgruppe,

eine Cyclo(C_3 - C_8) alkyl(C_1 - C_6) alkylgruppe,

eine Dicyclo(C_3 - C_9) alkyl(C_1 - C_5) alkylgruppe,

eine Bicyclo(C_6 - C_9) alkylgruppe,

eine Tricyclo(C_9 - C_{12}) alkylgruppe, bei der die Cycloalkylgruppe oder Cycloalkylfunktionalität in allen Fällen optional durch ein oder zwei aus der aus (C_1 - C_6) Alkyl, Hydroxy, Amino, Acetoxy, Acetamido, Phenyl, Benzoyloxy, Dimethylaminophenyl und Methylendioxyphenyl bestehenden Gruppe ausgewählten Substituenten substituiert sein können, die weiter mit einem Benzolring verbunden sein können,

eine Arylgruppe, eine Aryl(C_1 - C_6) alkylgruppe,

eine Diaryl(C_1 - C_6) alkylgruppe,

wobei die Arylgruppe oder die Arylfunktionalität in allen Fällen optional durch ein, zwei oder drei aus der aus (C_1 - C_6) Alkyl, (C_1 - C_6) Alkoxy, Halogen, Nitro, Hydroxy, Amino, Dimethylamino, Methylendioxy und Pyrrolidinyl bestehenden Gruppe ausgewählten Substituenten optional substituiert ist,

eine heterocyclische Gruppe oder eine an eine (C_1 - C_6) Alkylkette gebundene heterocyclische Gruppe,

wobei die heterocyclische Gruppe in allen Fällen eine gesättigte oder ungesättigte, 5- bis 8-gliedrige, monocyclische oder bicyclische, heterocyclische Gruppe wiedergibt, die 1 bis 3 Heteroatome enthält, die aus der aus S, O und N bestehenden Gruppe ausgewählt sind, und die heterocyclische Gruppe optional durch einen oder zwei Substituenten substituiert ist, die aus der aus Acetyl, Hydroxy, (C₁-C₉)Alkyl, (C₁-C₉)Alkyloxy, Cyclo(C₃-C₈)alkyl, Cyclo(C₃-C₈)alkyl(C₃-C₁₀)alkyl, Pyridyl(C₁-C₆)alkyl, Phenyl, Phenyl(C₁-C₆)alkyl, Diphenyl(C₁-C₆)alkyl und Phenylpiperazinyl bestehenden Gruppe ausgewählt sind, wobei die Phenylgruppe oder die Phenylfunktionalität optional durch ein oder zwei aus der aus Halogen, Hydroxy, (C₁-C₆)Alkyl, (C₁-C₆)Alkoxy, Cyano, Diethylamino und Trifluormethyl bestehenden Gruppe ausgewählt ist, die weiter mit einem Benzolring verbunden sein kann,

und R₃ und R₄ ferner, zusammen mit dem Stickstoffatom an das sie gebunden sind, eine gesättigte oder ungesättigte heterocyclische Gruppe bilden können,

wobei die heterocyclische Gruppe einen 5- bis achtgliedrigen, monocyclischen oder bicyclischen Ring wiedergibt, eine heterocyclische Gruppe oder eine von einer heterocyclischen Spiro-Verbindung abgeleitete Gruppe, die ein oder zwei aus der aus S, O oder N bestehenden Gruppe ausgewählte Heteroatome enthalten kann, die heterocyclische Gruppe optional durch ein oder zwei Substituenten substituiert ist, die aus der Gruppe bestehend aus (C₁-C₆)Alkyl, Hydroxy, Hydroxy(C₁-C₆)alkyl, (C₁-C₆)Alkoxy(C₁-C₆)alkyl, Acetoxy(C₁-C₆)alkyl, (C₁-C₉)Alkylcarbonyl, (C₁-C₆)Alkoxycarbonyl, Amino, Tosyl, Phenyl, Halogenphenyl, (C₁-C₆)Alkoxyphenyl, Phenyl(C₁-C₆)alkyl, Benzyloxy, Benzyloxy(C₁-C₆)alkyl, Toly, Xylyl, Benzoyl, Methylendioxyphenyl(C₁-C₆)alkyl, Pyridyl, Pyridylcarbonyl, Piperidyl, Pyrrolidinyl(C₁-C₆)alkyl und Pyrrolidinylcarbonyl(C₁-C₆)alkyl, die ferner mit einem Benzolring verbunden sein können,

wobei in allen Fällen die Alkyl- und Alkoxyfunktionalitäten entweder gerade oder verzweigt sein können, unter der Voraussetzung, daß beide, R₃ und R₄, nicht gleichzeitig ein Wasserstoffatom wiedergeben;

R₅ und R₆, die gleich oder verschieden sein können, jeweils eine gerade oder verzweigte (C₁-C₆)Alkylgruppe wiedergeben; und der Strich



-CH₂-CH₂- oder CH=CH- wiedergibt.

2. Verbindung gemäß Anspruch 1, worin R₃ und R₄, die gleich oder verschieden sein können, jeweils ein Wasserstoffatom wiedergeben,

eine gerade oder verzweigte (C₁-C₁₀)Alkylgruppe,
 eine gerade oder verzweigte (C₃-C₁₇)Alkenylgruppe,
 eine (C₁-C₄)Alkoxy(C₁-C₄)alkylgruppe,
 eine (C₁-C₄)Alkoxycarbonyl(C₁-C₄)alkylgruppe,
 eine Benzyloxycarbonyl(C₁-C₄)alkylgruppe, in der die Alkyfunktionalität optional durch Phenyl substituiert ist,
 eine (C₁-C₄)Alkylthio(C₁-C₄)alkylgruppe,
 eine Cyclo(C₃-C₁₂)alkylgruppe oder
 eine Cyclo(C₅-C₇)alkyl(C₁-C₄)alkylgruppe, in der die Cycloalkylgruppe oder die Cycloalkylfunktionalität optional monosubstituiert ist durch einen Substituenten, ausgewählt aus der Gruppe bestehend aus (C₁-C₄)Alkyl, Hydroxy, Amino, Acetoxy, Acetamid, Phenyl, Benzyloxy, Dimethylaminophenyl und Methylendioxyphenyl, oder die Cycloalkylgruppe oder die Cycloalkylfunktionalität optional mit einem Benzolring verbunden ist;
 eine Dicyclohexyl(C₁-C₄)alkylgruppe, eine Bicyclooctylgruppe, eine Adamantylgruppe, eine Phenylgruppe, optional substituiert durch (C₁-C₄) Alkyl oder Hexyloxy,
 eine Naphthylgruppe,
 eine Anthrylgruppe,
 eine Phenyl(C₁-C₄)alkylgruppe in der die Phenylfunktionalität optional durch ein oder zwei Substituenten substituiert ist, die aus der aus (C₁-C₄)Alkyl, (C₁-C₄)Alkoxy, Halogen, Nitro, Hydroxy, Amino, Dimethylamino, Methylendioxy und Pyrrolidinyl bestehenden Gruppe ausgewählt sind;
 eine Diphenyl(C₁-C₄)alkylgruppe, eine heterocyclische Gruppe oder eine heterocyclische Gruppe die an eine (C₁-C₄)Alkylkette gebunden ist, in der die heterocyclische Gruppe einen gesättigten oder ungesättigten, 5- oder 6-gliedrigen monocyclischen oder bicyclischen Ring wiedergibt, wobei die heterocyclische Gruppe 1 oder 2 Stickstoffatome enthält und die heterocyclische Gruppe optional durch ein oder zwei Substituenten substitu-

iert ist, die aus der aus Acetyl, Hydroxy, (C₁-C₆)Alkyl, Cyclohexyl, Pyridyl(C₁-C₄)alkyl, Phenyl(C₁-C₄)alkyl oder Diphenyl(C₁-C₄)alkyl, ausgewählt sind, wobei die Phenylfunktionalität optional durch ein oder zwei Substituenten substituiert ist, die aus der aus Halogen(C₁-C₄)alkyl, (C₁-C₄)Alkoxy, Cyano, Diethylamino und Triflourmethyl und Phenylpiperazinyl bestehenden Gruppe ausgewählt sind, die ferner mit einem Benzolring verbunden sein kann;

und ferner R₃ und R₄, zusammen mit dem Stickstoffatom, an das sie gebunden sind, einen gesättigten oder ungesättigten heterocyclischen Ring bilden können, wobei die heterocyclische Gruppe einen 5- bis 7-gliedrigen, mono- oder bicyclischen Ring wiedergibt, eine heterocyclische Gruppe oder eine von einer heterocyclischen Spiro-Verbindung abgeleiteten Gruppe, die ein oder zwei Stickstoffatome enthält, wobei die heterocyclische Gruppe optional durch ein oder zwei Substituenten substituiert ist, die aus der aus (C₁-C₄)Alkyl, Hydroxy(C₁-C₄)alkyl, Acetoxy(C₁-C₄)alkyl, (C₁-C₆)Alkylcarbonyl, (C₁-C₄)Alkoxycarbonyl, Tosyl, Phenyl, Phenyl(C₁-C₄)alkyl, Benzyloxy, Benzyloxy(C₁-C₄)alkyl, Benzoyl, Methylendioxyphenyl(C₁-C₄)alkyl, Pyridylcarbonyl, Piperidyl und Pyrrolidinylcarbonyl(C₁-C₄)alkyl bestehenden Gruppe ausgewählt sind.

3. Verbindung gemäß Anspruch 2, wobei R₃ und R₄, die gleich oder verschieden sein können, jeweils ein Wasserstoffatom wiedergeben, eine gerade oder verzweigte (C₁-C₇)Alkylgruppe, eine Cyclo(C₄-C₈)alkylgruppe, eine heterocyclische Gruppe oder eine an eine (C₁-C₄)Alkylenkette gebundene heterocyclische Gruppe, wobei die heterocyclische Gruppe einen gesättigten oder ungesättigten, 5- oder 6-gliedrigen, monocyclischen oder bicyclischen Ring wiedergibt, eine ein Stickstoffatom enthaltende heterocyclische Gruppe und die heterocyclische Gruppe optional mit einem oder zwei Substituenten substituiert ist, ausgewählt aus der Gruppe bestehend aus Methyl, Ethyl, Cyclohexyl, Pyridylmethyl und Phenyl(C₁-C₃)alkyl, wobei die Phenylfunktionalität optional durch ein oder zwei Substituenten substituiert ist, die aus der Gruppe bestehend aus Halogen, Methoxy, Cyano, Dimethylamino und Triflourmethyl besteht, die ferner mit einem Benzolring verbunden sein kann.

4. Verbindung gemäß Anspruch 3, wobei R₃ und R₄, die gleich oder verschieden sein können, jeweils ein Wasserstoffatom wiedergeben, eine gerade oder verzweigte (C₁-C₄)Alkylgruppe, Cyclohexyl, Cycloheptyl, Pyrrolidinyl oder Piperidyl, wobei die letztgenannten beiden heterocyclischen Gruppen optional mit einem oder zwei Substituenten substituiert sind, die aus der Gruppe bestehend aus Methyl, Ethyl, Cyclohexyl, Pyridylmethyl und Phenyl(C₁-C₃)alkyl ausgewählt sind, wobei die Phenylfunktionalität optional mit einem oder zwei Substituenten substituiert ist, ausgewählt aus der aus Halogen, Methoxy, Cyano, Diethylamino und Triflourmethyl bestehenden Gruppe, die ferner mit einem Benzolring verbunden sein kann.

5. Verbindung gemäß Anspruch 2, wobei R₃ und R₄, zusammen mit dem Stickstoffatom, an das sie gebunden sind, einen gesättigten oder ungesättigten heterocyclischen Ring bilden können, wobei die heterocyclische Gruppe eine 5- oder 6-gliedrige, monocyclische oder bicyclische, heterocyclische Gruppe wiedergibt, die ein oder zwei Stickstoffatome enthält, wobei die heterocyclische Gruppe optional mit einem oder zwei Substituenten substituiert ist, die aus der Gruppe bestehend aus Methyl, Hydroxyethyl, Acetoxyethyl, Pentylcarbonyl, Ethoxycarbonyl, Tosyl, Phenyl, Benzyl, Benzyloxy, Benzyloxyethyl, Benzoyl, Methylendioxybenzyl, Pyridylcarbonyl und Piperidyl ausgewählt sind, wobei diese ferner mit einem Benzolring verbunden sein können.

6. Verbindung gemäß Formel (I) oder einem pharmazeutisch verträglichen Salz davon, wie in einem der Ansprüche 1 bis 5 beansprucht, zur Verwendung in der Therapie.

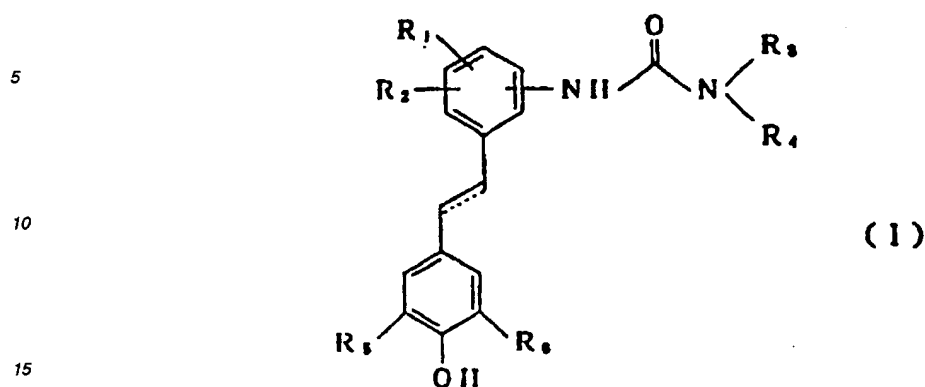
7. Verbindung, wie in Anspruch 6 beansprucht, zur Verwendung bei der ACAT-Inhibierung.

8. Pharmazeutische Zusammensetzung, als aktiven Bestandteil eine Verbindung der Formel (I) oder ein pharmazeutisch verträgliches Salz davon, wie in einem der Ansprüche 1 bis 5 beansprucht, und einen pharmazeutisch verträglichen Träger und/oder Hilfsstoff enthaltend.

9. Verwendung einer Verbindung der Formel (I) oder eines pharmazeutisch verträglichen Salzes davon, wie in einem der Ansprüche 1 bis 5 beansprucht, zur Herstellung eines Medikaments zur Prophylaxe und Behandlung von Hypercholesterolemie und Atherosklerose.

Revendications

1. Composé de la formule (I) ou un sel pharmaceutiquement acceptable de celui-ci :



dans laquelle :

20

R_1 et R_2 , qui peuvent être identiques ou différents, représentent chacun

25

- un atome d'hydrogène,
- un atome d'halogène,
- un groupe (C₁-C₆)alcoyle droit ou ramifié, ou
- un groupe (C₁-C₆)alcoxy droit ou ramifié,

R_3 et R_4 , qui peuvent être identiques ou différents, représentent chacun

30

- un atome d'hydrogène,
- un groupe (C₁-C₁₂)alcoyle droit ou ramifié,
- un groupe (C₂-C₂₀)alcényle droit ou ramifié,
- un groupe (C₁-C₆)alcoxy(C₁-C₆)alcoyle,
- un groupe (C₁-C₆)alcoxycarbonyl(C₁-C₉)alcoyle,
- un groupe benzyloxycarbonyl(C₁-C₆)alcoyle, dans lequel la fraction alcoyle est facultativement substituée par un phényle,
- un groupe N,N-di(C₁-C₆)alcoylamino(C₁-C₆)alcoyle,
- un groupe N-(C₁-C₆)alcoyl-N-benzylamino(C₁-C₆)alcoyle,
- un groupe (C₁-C₆)alcoylthio(C₁-C₆)alcoyle,
- un groupe oxo(C₁-C₉)alcoyle,
- un groupe hydroxy(C₁-C₆)alcoyle,
- un groupe dihydroxy(C₁-C₆)alcoyle,
- un groupe cyclo(C₃-C₁₅)alcoyle,
- un groupe cyclo(C₃-C₈)alcoyl(C₁-C₆)alcoyle,
- un groupe dicyclo(C₃-C₉)alcoyl(C₁-C₆)alcoyle,
- un groupe bicyclo(C₆-C₉)alcoyle,
- un groupe tricyclo(C₉-C₁₂)alcoyle,

50

dans lesquels, dans tous les cas, le groupe cycloalcoyle ou la fraction cycloalcoyle est facultativement substitué par un ou deux substituants sélectionnés dans le groupe comprenant un alcoyle à 1 à 6 atomes de carbone, hydroxy, amino, acétoxy, acétamido, phényle, benzyloxy, diméthylaminophényle et méthylènedioxyphényle, qui peuvent être en outre fusionnés avec un cycle benzénique,

55

- un groupe aryle,
- un groupe aryl(C₁-C₆)alcoyle,
- un groupe diaryl(C₁-C₆)alcoyle,
- dans lesquels, dans tous les cas, le groupe aryle ou la fraction aryle est facultativement substitué par un, deux ou trois substituants sélectionnés dans le groupe comprenant (C₁-C₆)alcoyle, (C₁-C₆)alcoyloxy, halogène, nitro, hydroxy, amino, diméthylamino, méthylènedioxy et pyrrolidinyle,
- un groupe hétérocyclique, ou
- un groupe hétérocyclique attaché à une chaîne (C₁-C₆)alcoylène,

dans lesquels, dans tous les cas, le groupe hétérocyclique représente un groupe hétérocyclique, monocyclique ou bicyclique, d'un cycle à 5 à 8 membres saturé ou insaturé, contenant 1 à 3 hétéroatomes choisis dans le groupe comprenant S, O et N, et le groupe hétérocyclique est facultativement substitué par un ou deux substituants choisis dans le groupe comprenant les suivants : acétyle, hydroxy, (C₁-C₆)alcoyle, (C₁-C₉)alcoyloxy, cyclo(C₃-C₈)alcoyle, cyclo(C₃-C₈)alcoyl(C₃-C₁₀)alcoyle, pyridyl(C₁-C₆)alcoyle, phényle, phényl(C₁-C₆)alcoyle, diphényl(C₁-C₆)alcoyle et phénylpipérazinyle, le groupe phényle ou la fraction phényle étant facultativement substitué par un ou deux substituants choisis dans le groupe comprenant les suivants : halogène, hydroxy, (C₁-C₆)alcoyle, (C₁-C₆)alcoxy, cyano, diéthylamino et trifluorométhyle, qui peuvent en outre fusionner avec un cycle benzénique, et en outre

R₃ et R₄, ensemble avec l'atome d'azote sur lequel ils sont attachés, peuvent former un groupe hétérocyclique saturé ou insaturé,

dans lequel le groupe hétérocyclique représente un groupe hétérocyclique, monocyclique ou bicyclique à cycle à 5 à 8 membres, ou un groupe dérivé d'un composé spiro hétérocyclique, qui peut contenir un ou deux hétéroatomes choisis dans le groupe comprenant S, O, et N, le groupe hétérocyclique étant facultativement substitué par un ou deux substituants choisis dans le groupe comprenant les suivants : (C₁-C₆)alcoyle, hydroxy, hydroxy(C₁-C₆)alcoyle, (C₁-C₆)alcoxy(C₁-C₆)alcoyle, acétoxy(C₁-C₆)alcoyle, (C₁-C₉)alcoylcarbonyle, (C₁-C₆)alcoxycarbonyle, amino, tosyle, phényle, halogénophényle, (C₁-C₆)alcoxyphényle, phényl(C₁-C₆)alcoyle, benzyloxy, benzyloxy(C₁-C₆)alcoyle, tolyle, xylyle, benzoyle, méthylènedioxyphényl(C₁-C₆)alcoyle, pyridyle, pyridylcarbonyle, pipéridyle, pyrrolidinyl(C₁-C₆)alcoyle et pyrrolidinylcarbonyl(C₁-C₆)alcoyle, qui peuvent être en outre fusionnés avec un cycle benzénique, dans lesquels, dans tous les cas, les fractions alcoyle et alcoxy peuvent être, soit droites, soit ramifiées,

sous réserve que R₃ et R₄ ne représentent pas tous deux un atome d'hydrogène en même temps ;

R₅ et R₆, qui peuvent être identiques ou différents, représentent chacun un groupe (C₁-C₆)alcoyle droit ou ramifié ; et la ligne



représente -CH₂CH₂- ou -CH=CH-.

2. Composé selon la revendication 1, dans lequel R₃ et R₄, qui peuvent être identiques ou différents, représentent chacun :

- un atome d'hydrogène,
- un groupe (C₁-C₁₀)alcoyle droit ou ramifié,
- un groupe (C₃-C₁₇)alcényle droit ou ramifié,
- un groupe (C₁-C₄)alcoxy(C₁-C₄)alcoyle,
- un groupe (C₁-C₄)alcoxycarbonyle(C₁-C₄)alcoyle,
- un groupe benzyloxycarbonyl(C₁-C₄)alcoyle, où la fraction alcoyle est facultativement substituée par un phényle,
- un groupe (C₁-C₄)alcoylthio(C₁-C₄)alcoyle,
- un groupe cyclo(C₃-C₁₂)alcoyle, ou
- un groupe cyclo(C₅-C₇)alcoyl(C₁-C₄)alcoyle,

dans lesquels le groupe cycloalcoyle ou la fraction cycloalcoyle est facultativement monosubstitué par un substituant choisi dans le groupe comprenant les suivants : (C₁-C₄)alcoyle, hydroxy, amino, acétoxy, acétamide, phényle, benzyloxy, diméthylaminophényle et méthylènedioxyphényle, ou le groupe cycloalcoyle ou la fraction cycloalcoyle est facultativement fusionné avec un cycle benzénique ; un groupe dicyclohexyl(C₁-C₄)alcoyle, un groupe bicyclooctyle, un groupe adamantyle, un groupe phényle facultativement substitué par un (C₁-C₄)alcoyle ou hexyloxy, un groupe naphthyle, un groupe anthryle, un groupe phényl(C₁-C₄)alcoyle, dans lesquels la fraction phényle est facultativement substituée par un ou deux substituants choisis dans le groupe comprenant les suivants : (C₁-C₄)alcoyle, (C₁-C₄)alcoyloxy, halogène, nitro, hydroxy, amino, diméthylamino, méthylènedioxy et pyrrolidinyle ; un groupe diphényl(C₁-C₄)alcoyle, un groupe hétérocyclique ou un groupe hétérocyclique attaché sur une chaîne (C₁-C₄)alcoylène, dans lesquels le groupe hétérocyclique représente un groupe hétérocyclique monocyclique ou

- bicyclique à cycle à cinq à six éléments, saturé ou non saturé, contenant 1 ou 2 atomes d'azote, et le groupe hétérocyclique est facultativement substitué par un ou deux substituants choisis dans le groupe comprenant les suivants : acétyle, hydroxy, (C₁-C₆)alcoyle, cyclohexyle, pyridyl(C₁-C₄)alcoyle, phényl(C₁-C₄)alcoyle ou diphényl(C₁-C₄)alcoyle, dans lesquels la fraction phényle est facultativement substituée par un ou deux substituants choisis dans le groupe comprenant les suivants : halogène, (C₁-C₄)alcoyle, (C₁-C₄)alcoxy, cyano, diéthylamino et trifluorométhyle, et phénylpipérazinyle, qui peuvent être en outre fusionnés avec un cycle benzénique ; et en outre R₃ et R₄, ensemble avec l'atome d'azote sur lequel ils sont attachés, peuvent former un cycle hétérocyclique saturé ou insaturé, dans lequel le groupe hétérocyclique représente un groupe hétérocyclique, monocyclique ou bicyclique, à cycle à 5 à 7 éléments, ou un groupe dérivé d'un composé spiro hétérocyclique, qui contient un ou deux atomes d'azote, le groupe hétérocyclique étant facultativement substitué par un ou deux substituants choisis dans le groupe comprenant les suivants : (C₁-C₄)alcoyle, hydroxy(C₁-C₄)alcoyle, acétoxy(C₁-C₄)alcoyle, (C₁-C₄)alcoyl-carbonyle, (C₁-C₄)-alcoylcarbonyle, tosyle, phényle, phényl(C₁-C₄)alcoyle, benzyloxy, benzyloxy(C₁-C₄)alcoyle, benzoyle, méthylènedioxyphényl(C₁-C₄)alcoyle, pyridylcarbonyle, pipéridyle et pyrrolidinylcarbonyl(C₁-C₄)alcoyle.
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- 15 3. composé selon la revendication 2, dans lequel R₃ et R₄, qui peuvent être identiques ou différents, représentent chacun un atome d'hydrogène, un groupe (C₁-C₇)alcoyle droit ou ramifié, un groupe cyclo(C₄-C₈)alcoyle, un groupe hétérocyclique ou un groupe hétérocyclique attaché sur une chaîne (C₁-C₄)alkylène, dans lesquels le groupe hétérocyclique représente un groupe hétérocyclique, monocyclique ou bicyclique, à cycle à cinq ou six éléments, saturé ou insaturé, contenant un atome d'azote, et le groupe hétérocyclique est facultativement substitué par un ou deux substituants choisis dans le groupe comprenant les suivants : méthyle, éthyle, cyclohexyle, pyridylméthyle, et phényl(C₁-C₃)alcoyle, la fraction phényle étant facultativement substituée par un ou deux substituants choisis dans le groupe comprenant les suivants : atome d'halogène, méthoxy, cyano, diméthylamino et trifluorométhyle, qui peuvent être en outre fusionnés avec un cycle benzénique.
- 20
- 25 4. Composé selon la revendication 3, dans lequel R₃ et R₄, qui peuvent être identiques ou différents, représentent chacun un atome d'hydrogène, un groupe (C₁-C₄)alcoyle droit ou ramifié, cyclohexyle, cycloheptyle, pyrrolidinyle ou pipéridyle, les deux derniers groupes hétérocycliques étant facultativement substitués par un ou deux substituants choisis dans le groupe comprenant les suivants : méthyle, éthyle, cyclohexyle, pyridylméthyle, et phényl(C₁-C₃)alcoyle, la fraction phényle étant facultativement substituée par un ou deux substituants choisis dans le groupe comprenant un atome d'halogène et les groupes suivants : méthoxy, cyano, diéthylamino et trifluorométhyle, qui peuvent être en outre fusionnés avec un cycle benzénique.
- 30
- 35 5. Composé selon la revendication 2, dans lequel R₃ et R₄, ensemble avec l'atome d'azote auquel ils sont attachés, peuvent former un cycle hétérocyclique saturé ou insaturé, dans lequel le groupe hétérocyclique représente un groupe hétérocyclique, monocyclique ou bicyclique, à cycle à cinq ou six éléments, qui contient un ou deux atomes d'azote, le groupe hétérocyclique étant facultativement substitué par un ou deux substituants choisis dans le groupe comprenant les suivants : méthyle, hydroxyéthyle, acétoxyéthyle, pentylcarbonyle, éthoxycarbonyle, tosyle, phényle, benzyle, benzyloxy, benzyloxyéthyle, benzoyle, méthylènedioxybenzyle, pyridylcarbonyle et pipéridyle, qui peuvent être en outre fusionnés avec un cycle benzénique.
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6. Composé de la formule (I) ou sel pharmaceutiquement acceptable de ce composé, selon l'une des revendications 1 à 5, pour utilisation en thérapie.
- 45 7. Composé selon la revendication 6, utilisé dans l'inhibition de ACAT.
8. Composition pharmaceutique comprenant, comme ingrédient actif, un composé de la formule (I) ou un sel pharmaceutiquement acceptable de celui-ci selon l'une des revendications 1 à 5, et un support et/ou un excipient pharmaceutiquement acceptable.
- 50 9. Utilisation d'un composé de la formule (I) ou d'un sel pharmaceutiquement acceptable de celui-ci selon l'une des revendications 1 à 5, dans la fabrication d'un médicament pour la prophylaxie et le traitement de l'hypercholestérolémie et de l'athérosclérose.
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